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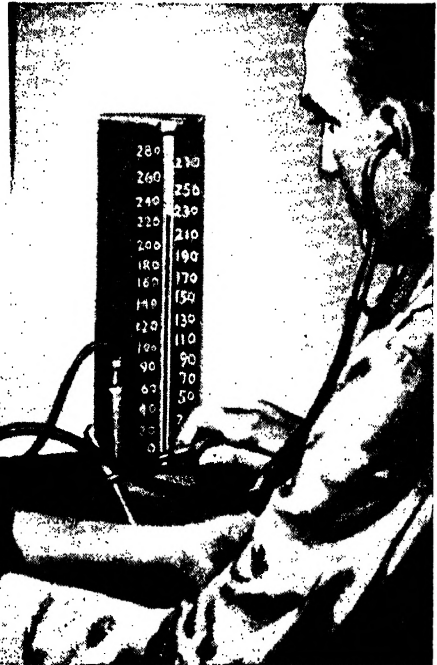
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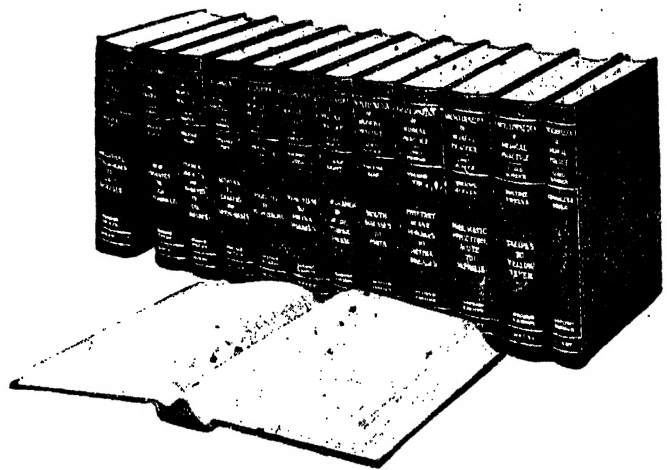
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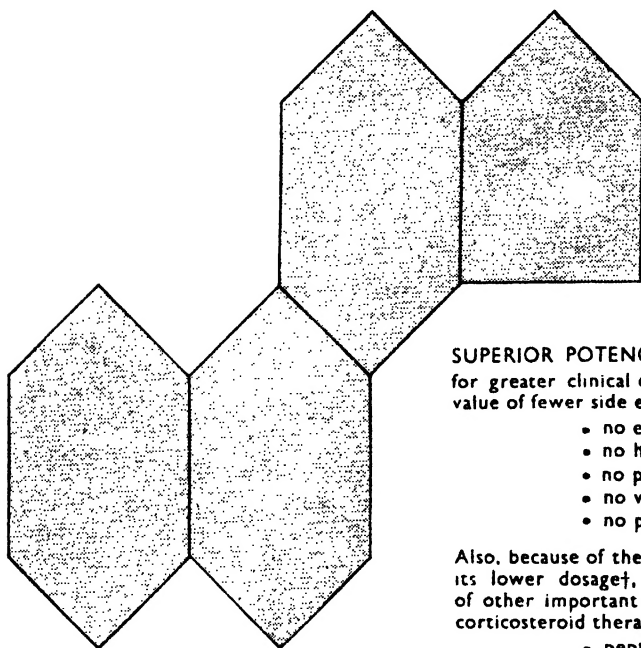
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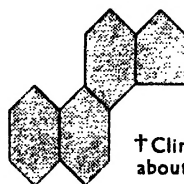
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A BUSY PRACTITIONER is often faced with the problem not only of curing his patients' ailments, but of advising them how to prevent the occurrence of such diseases. With the development of modern social medicine, the emphasis is being shifted from cure to prevention. The most effective way of preventing diseases—whether infective, deficiency or degenerative—is to maintain a well-nourished body, which alone means positive health.

A balanced diet is one which supplies enough energy for the type of life that a man leads and protects him from the various deficiencies and inadequacies of the dietary essentials. It should include adequate quantities of proteins, fats, carbohydrates, minerals, vitamins and water.

The recommended nutritional minimum of oil and fat consumption in India, according to the Nutrition Advisory Committee of the Indian Council of Medical Research, is two ounces per head per day, while what is actually available is only half an ounce. Fats, like butter and ghee, are good, but their supply is far short of requirements, and they are too expensive for the everyday use of most people. Our President, Dr. Rajendra Prasad, in one of his speeches, remarked: "Improvement in the milk field is a tremendous task, and is bound to be a slow process." Further, milk consumed as such is better than its products, like ghee and butter, because it provides, in addition to fat, animal protein as well as calcium and vitamins.

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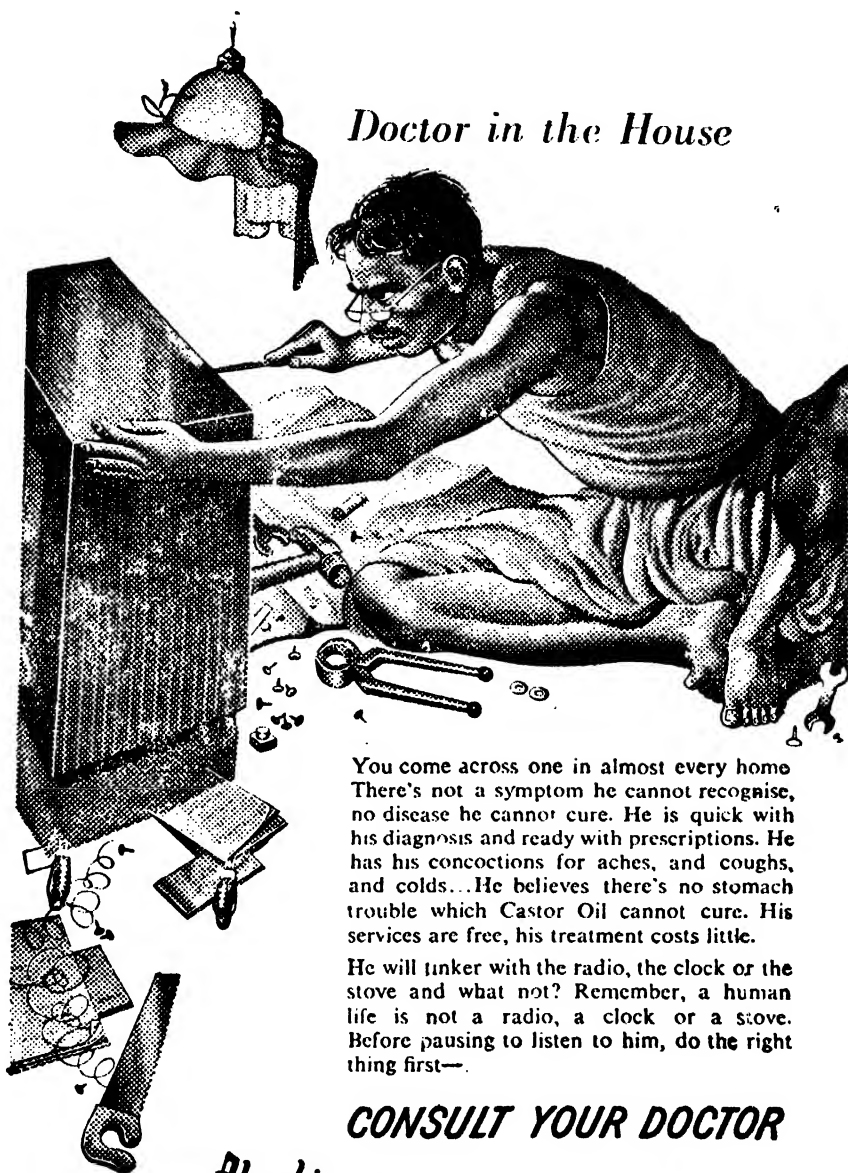
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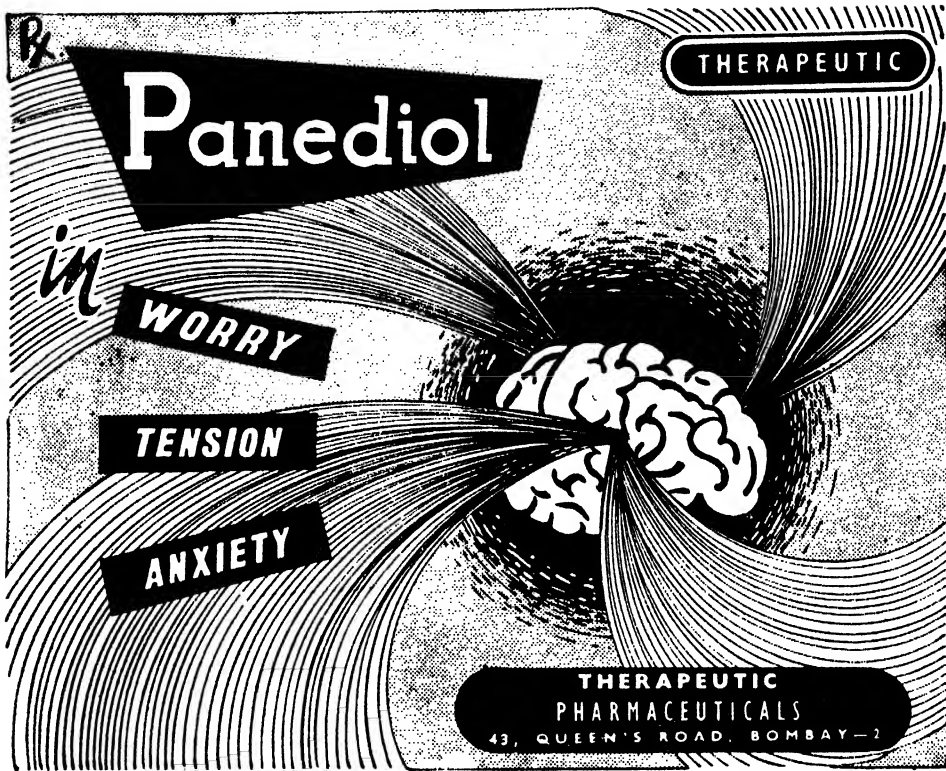
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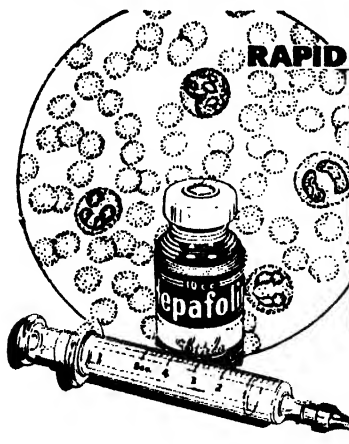
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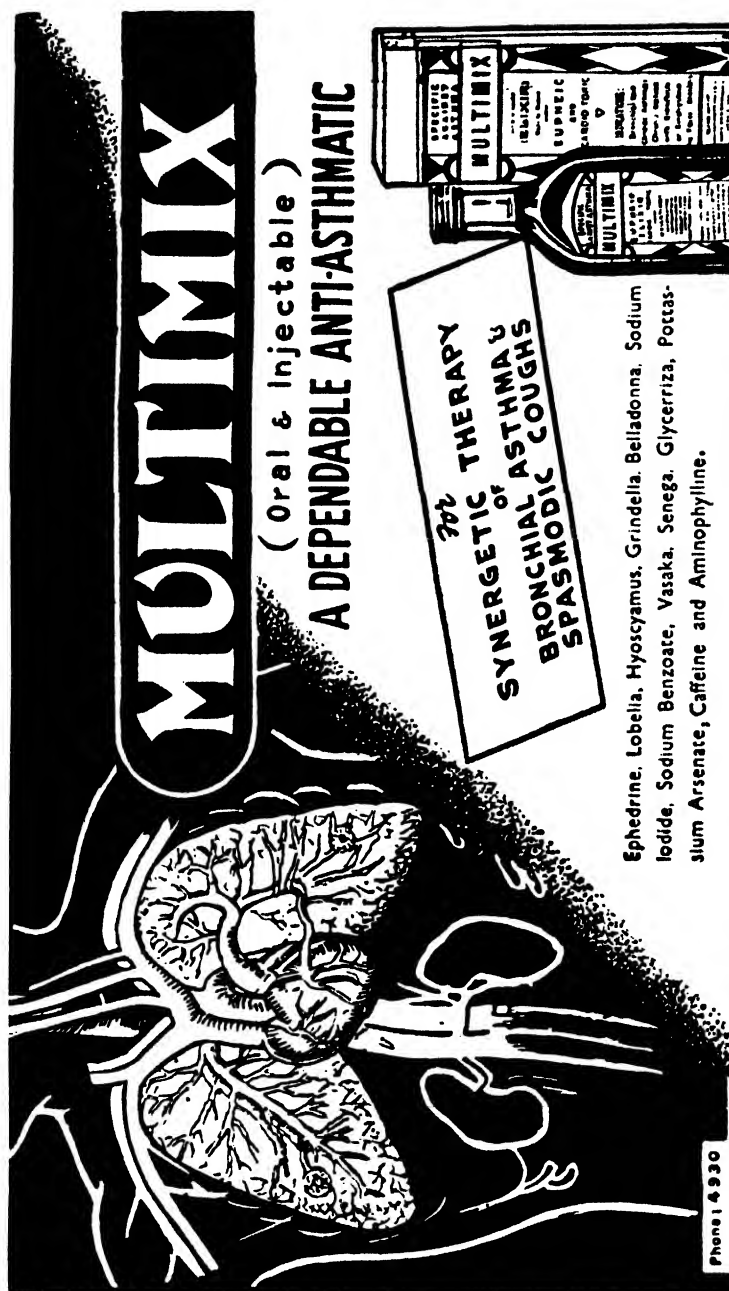
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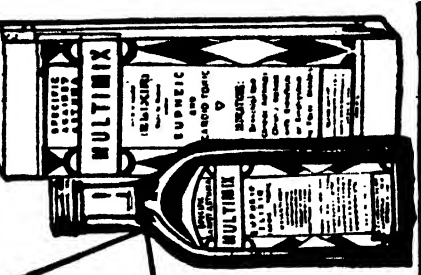
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## PREFACE

The publication of this Year-Book is an humble effort to add India's mite to the ever-increasing pool of modern scientific knowledge of the world, in the subject of medicine. This is the first effort of its kind by the Indian medical profession and we feel happy that this venture has received the co-operation of some of the most eminent medical persons in this country.

The publication has been carried out with two main objects. Firstly, to provide the Indian medical practitioner, within the compass of a single book, information on recent advances in the medical sciences. It is common knowledge that there are hundreds of doctors practising in rural areas who have very little touch with academic medicine, and no opportunities to attend refresher courses, symposia or lecture-demonstrations, a privilege which their colleagues enjoy in some of the main cities. On the other hand, there are many practitioners, who would have very little time to go through various textbooks and medical journals to glean information of use in their practice. We thought therefore, that India had to depend on her own medical profession in order to provide the needs of such practitioners.

Secondly, we had in mind that the contributors should include, as far as was possible, scientific material, the result of investigations and observations done in this country. This second object has been fulfilled to some extent, but in the future publications of this Year-Book more and more importance and emphasis would be given to it.

We are aware of many of our shortcomings. Some important subjects could not be covered in this book but we assure the reader that such would find their rightful place in the future editions. There has been a certain lack of uniformity in the presentation of various contributions and this particularly holds true for the lists of references. The references have been presented differently by different authors, but here again we would put in our best endeavour to do away with this discrepancy in the future. Lastly, we apologize for the delay in publication which could not be avoided despite our most sincere efforts.

The present Year-Book covers mostly review of scientific work in the various branches of medicine of the last few years. The future publications would cover the advances of each preceding year.

We hope that the readers will overlook any commissions or omissions that may have crept in the present volume.

We are also thankful to Dr. S. S. Thakur, M.D., for his assistance in editing some of the material.

We are indebted to the publishers who have been most helpful and co-operative in bringing out this Year-Book.

— Editors

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# INDIAN YEAR-BOOK

## OF

### MEDICAL SCIENCES - 1958

#### ABORTION

K. Bhasker Rao

Habitual abortions have worried obstetricians for decades. Javert<sup>1</sup> found in a series of 104 cases of habitual abortions that 12 per cent had retroversion of the uterus, 20 per cent had myomas, 3 had double uteri and in most cases no cause could be given. But with early and most frequent prenatal care, with a diet rich in citrus fruits, with vitamins C, P and K supplements, calcium and thyroid, and withholding the sex hormones and complete sex abstinence, abortion took place in only 16 per cent of 150 pregnancies; whereas, in the same group, 95 per cent of 420 pregnancies had ended in abortions before. Jeffcoate<sup>2</sup> found that in large number of habitual abortions and premature labour no organic cause could be discovered. After a study of hystero-grams taken 10-16 weeks after delivery in those who had normal labour and those who had repeated abortions or premature labour, he concluded that in 44 out of 69 patients belonging to the latter group there was a 'funnel cervix' without demarcation between the uterine cavity and cervical canal. This gaping cervix may result from acquired or congenital causes and in most of his patients there was no history of any trauma either operative or at childbirth. He suggests that in such cases, reconstruction operations of internal os between or during pregnancies could be tried by passing silver wire, silk, nylon or even fascial strip around the cervix beneath the vaginal skin.

**Threatened Abortions :** Arborization or palm-leaf (PL) pattern of the cervical mucus is normally seen in 90 per cent of normal non-pregnant women, but is not found in early pregnancy. A positive PL test in early pregnancy should be a warning of threatened abortion or ectopic gestation. In 226 patients studied in the first trimester by Zondek et al<sup>3</sup>, 200 were negative and 26 positive ; of the latter, 15 aborted and 2 were ectopics. The outcome of pregnancy in threatened abortion cases has been studied by Turnbull and Walker<sup>4</sup>. Out of 115 such cases who left the hospital, 19 per cent aborted later and in the remaining, antepartum haemorrhage was found to be thrice as common as in the hospital average and the foetal abnormality was twice as great, probably due to the damage of the deciduoplacental site at the time of initial bleeding.

**Legalisation of Abortions<sup>5</sup> :** In view of the circumstances under which induced abortions (criminal) are done, the morbidity and mortality rates in these cases have been always high. Before 1920, in Russia, 50 per cent of the criminal abortions used to be infected and 4 per cent of those ended fatally. So between 1920-1936, abortion was legalised and was done only in the hospital by a doctor. It became illegal if done outside or money was accepted. Abortion rate was increased as a result but mortality rate was nil in Moscow, and elsewhere it was 0.74 per cent. From 1936 to 1955, again it was declared illegal to induce abortions except for therapeutic reasons. But owing to the harm caused by criminal abortions, abortion has been again legalised from November 1955, but to be induced only by a specialist and that too only in a hospital.

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## Achalasia of the Cardia

**ACCIDENTAL HAEMORRHAGE**—See HAEMORRHAGE, ACCIDENTAL

## ACHALASIA OF THE CARDIA

*R. Mahadevan*

The cause of this condition still remains unknown. The original term "cardiospasm" signified a spasm of the cardiac sphincter and as this explanation was not considered satisfactory, the term "achalasia", signifying failure of relaxation of the normal cardiac sphincter was considered more appropriate and came to be used more frequently. But many think that this term is to be considered more as an alternative title, rather than as one explaining the aetiology more accurately. The point is that there is no organic obstruction in achalasia, and whatever the aetiology it accounts for 20 per cent of cases of dysphagia (Vineberg, 1956). Inflammation, psychic influences, autonomic imbalance, diaphragmatic pinchcock effect at the oesophageal hiatus, active dilatation of the oesophagus, vitamin B<sub>1</sub> deficiency etc. continue to be suggested as aetiological factors, none of which however is wholly satisfactory. The motor innervation of the oesophagus is vagal. An oesophageal dilatation indistinguishable from cardiospasm has followed vagus injury, post-diphtheritic paralysis of vagus and lead poisoning. Ian Aird reports of a temporary but radiologically demonstrable form after vagotomy (1957). Some cases seem to be of reflex origin, associated with peptic ulcer, asthma and gall-bladder disease. Oesophageal dilatation indistinguishable from cardiospasm has been described in children after whooping cough.

The changes in the oesophagus, first of hypertrophy, followed by dilatation, and the effects of stagnation resulting in ulceration of mucous membrane, spill-over infection, etc. are well-known. Degeneration and disappearance of the Auerbach's plexus is now considered to be the result of the strangling effect of chronic inflammation and fibrosis and not a cause of the condition.

In some cases well-developed achalasia may be present without the patient having any dysphagia, the oesophagus accommodating the contents comfortably and allowing a "natural drip feed through the cardia" (Allison, quoted by Aird). More often, the patient is able to swallow easily at the beginning of the meal, but soon experiences a sense of fullness behind the lower sternum. The symptoms of dysphagia are aggravated by rapid eating, excessive roughage and hot or cold fluids (Vineberg). But I know of one lady aged 47 who, however, was able to get relief and swallow more easily by taking warm fluids along with morsels of food. Carcinoma had been excluded in her by more than one oesophagoscopy examination and by several skiagrams at different clinics. Sometimes, the patient learns the trick of forcing food into the stomach by flexing the chin on the sternum, gripping the chest with both hands and expiring forcefully. This manoeuvre is not free from danger and spontaneous pneumothorax has occurred after it (Aird, 1957). The stagnating food may regurgitate and must not be mistaken for vomiting. The oesophagus may slowly dilate to an enormous size and I know of at least one case where the dilated oesophagus occupied practically the entire chest. Nocturnal regurgitation may be very distressing and spill-over infection may result in aspiration pneumonia or lung abscess. Sometimes, the underlying cause of lung trouble may be altogether missed and achalasia of cardia may be mistaken for respiratory diseases, particularly in children and adolescents. A wide variety of respiratory disorders ranging from an irritant cough and a "tickle in the throat" to severe pulmonary infections, lung fibrosis and lipoid pneumonia may arise, overshadowing the primary cause (Davies et al). The same authors also point out that acid-fast saprophytes in the sputum may be mistaken for tubercle bacilli and refer to a series where pulmonary complications were found in 63 out of 601 cases, detailing three illustrative cases of their own, two in children and one in an adolescent of 18. One of them, a boy of 13, had haemoptysis at the onset. In this boy, the onset was with cough, haemoptysis and vomiting and later he had features simulating bronchiectasis. In long-standing cases of achalasia toxic absorption may result in osteoarthropathy. Pain may or may not be present. At times the pain may be severe and even colicky in nature. It is said that where hypertrophy of the oesophagus is pronounced, pain may occur, whereas, in cases where the oesophagus may give way to dilatation and the wall is thinned out, pain may be absent. It has been suggested that there are two types, one with pain and another without (D'Abreu, 1953).

The diagnosis of cardiospasm must always be confirmed by oesophagoscopy and the possibility of the underlying cause being carcinoma must always be remembered and this can only be excluded by oesophagoscopy, irrespective of the age of the patient, duration of symptoms, etc. I have seen some cases of carcinoma of oesophagus in patients aged 25 or even less and the danger of the

## PLATE 1

### ACHALASIA OF THE CARDIA

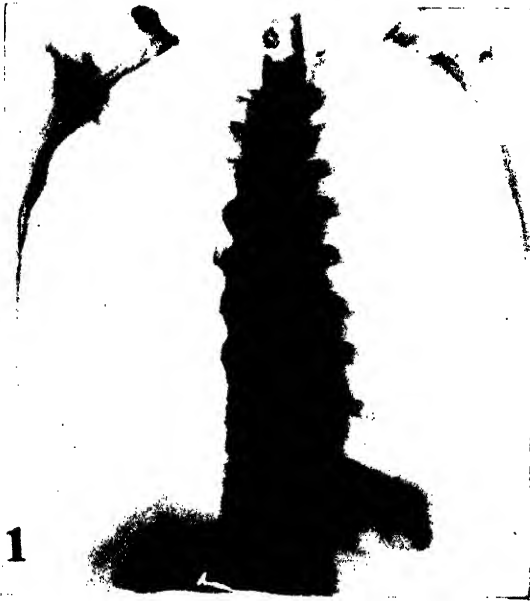


FIG. 1

*Ba swallow skiagram, P-A view, showing smooth filling defect in the lower end of the oesophagus. This patient was a man of 45, who had been diagnosed and treated elsewhere as achalasia of the cardia, without any relief. Oesophagoscopic examination did not show any tumour in the oesophagus. However, at operation he was found to have carcinoma of the cardiac end of the stomach. (The smooth indentation in the mid-oesophagus is due to a prominent aortic knob).*



FIG. 2

*Ba swallow skiagram, oblique view, in a young man of 24, with achalasia of the cardia. Note the dilated oesophagus and smooth filling defect at its lower end and the absence of gas bubble in the fundus of the stomach.*

*PLATE II*

ACHALASIA OF THE CARDIA



*Same case as in Fig. 2 after Heller's operation. Post-operative Ba swallow skiagram, oblique view. Note reappearance of gas bubble in the fundus of the stomach. After successful treatment, reappearance of the gas bubble will be evident and indeed is a test for the efficiency of any treatment adopted. Note that even after successful operation and relief of symptoms, the dilatation of the oesophagus is still persisting*

FIG. 3

condition being assumed to be achalasia in the young is really great. I have known more than one case sent in as achalasia and which had been treated as such for a good length of time, when oesophagoscopy unmistakably showed carcinoma (Fig. 1). Such mistakes are due to too much stress being laid on the differences in the radiological appearances of the two conditions. Emphasis should rather be on the fact that even if barium meal skiagrams show a smooth filling defect, and the oesophagus dilated it could still be a carcinoma (Mahadevan, 1957). A circumferential submucous infiltration of carcinoma of the lower end of the oesophagus or of the gastric cardia may give a picture indistinguishable from that of achalasia of the cardia. In achalasia, the gas bubble in the fundus of the stomach will be absent though its outline may be otherwise normal in the barium meal skiagrams. After successful treatment reappearance of the gas bubble will be evident, and indeed is a test for the efficacy of any treatment adopted (Figs. 2 & 3).

Treatment in the established cases is mainly surgical. Hurst bougies, Plummer's or Negus hydrostatic dilators used under oesophagoscopic vision, all have an established place; but if these fail, operation must be considered. At least at the first time of dilatation a straight X-ray must be taken to ensure that the bougie has entered the stomach and is not merely lying curled up in the dilated oesophagus. Further, locating the cardiac end of the oesophagus by oesophagoscopic vision in the dilated distorted oesophagus is not easy, and dilatation even under oesophagoscopic vision is not without danger.

Of the various operative procedures suggested, e.g., Heller's operation, sympathectomy, Mikulicz's retrograde dilatation, cardioplasty, oesophagogastrostomy, Heller's operation of oesophagocardiomyotomy is the safest and the best. This can be done either by a left thoracotomy or by a high left paramedian incision running up to the base of the xiphisternum with resection of the xiphisternum if exposure is inadequate. The abdominal route is easy, and moreover affords an opportunity for examining the abdominal contents. Further, thoracotomy definitely causes a higher mortality than laparotomy. Reversed Trendelenburg position of the patient gives excellent exposure and good lighting focussed on the operative field renders the procedure easier. The incision through the oesophagus and stomach is made through the muscular coat until the submucous plane is reached. This incision should centre on the gastro-oesophageal junction and should extend for an inch on either side of it. The muscle fibres are made to retract with a little blunt dissection. The mucosa should bulge freely along the whole length of the gap but should not be opened. Some surgeons have observed an encircling fibrotic band in making the oesophageal incision and have expressed the view that the existence of such a band may be of aetiological significance.

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**ACTH**—See **HORMONES, STEROID**

**ADENOMA OF BRONCHUS**—See **BRONCHUS, ADENOMA OF**

**ADOLESCENT HEALTH**—See **CHILD AND ADOLESCENT HEALTH**

#### ADRENAL CORTEX

*B. B. Mukherji*

*Corticosteroid Hormones:* These have been discussed in another section of this book by T. S. Row.

*Treatment of Adrenocortical Deficiencies:* This has been completely revolutionised with the advent of the new adrenocortical steroids. Hart<sup>1</sup> has reviewed the subject and reported



## Adrenal Cortex

the result of his studies in treatment of adrenocortical deficient subjects. Since adrenal substitution therapy has been a practical measure, subtotal and total adrenalectomy is being performed in an increasing number of disorders such as Cushing's syndrome, metastatic malignant disease and malignant hypertension. It has also been empirically carried out in certain other disorders such as diabetes mellitus, schizophrenia and rheumatoid arthritis. The clinical material which formed the basis of study of Hart consisted of 150 patients, 5 adrenalectomized for malignant hypertension, 2 for Cushing's syndrome and 143 for metastatic malignant disease. He found that in maintenance of adrenocortical deficiency states, cortisone (or hydrocortisone) is now the most important single therapeutic agent. Doses of 37.5 to 50 mg daily are necessary for full substitution therapy. Cortisone in the above dosage will often be enough to maintain the patient in good health. When any salt-retaining substance has been needed, the author has used 9  $\alpha$ -fluoro-hydrocortisone in addition to cortisone and has found it very useful. In crisis intravenous hydrocortisone or flurohydrocortisone is the drug of choice. However, the use of flurohydrocortisone and cortisone orally in adequate dosage at the first sign of adrenocortical deficiency has greatly reduced the incidence of crisis.

Nabarro and Walker<sup>2</sup> have studied and reported their experiences in the treatment of 9 cases of Addison's disease and of 30 patients who had undergone total adrenalectomy. Cortisone given orally in dosage of 37.5 to 50 mg daily formed the basis of substitution therapy. It was found that one-third of the patients with 37.5 mg and one-tenth of those with 50 mg became sodium-depleted. The addition of oral 9  $\alpha$ -flurohydrocortisone 0.1 to 0.2 mg a day was found an effective way of correcting the salt depletion.

*Prednisone and Prednisolone* : These have been discussed in another section of this book by V. Iswariah.

*Cushing's Syndrome* : Querido and Van Seters<sup>3</sup> have described the symptomatology and therapy in 28 cases of this syndrome. Symptoms vary widely from case to case. Full-moonface, flushed complexion, typical habitus, hypertrichosis, headache, general weakness, backache and oligomenorrhoea or amenorrhoea form the basic pattern of the syndrome. Investigations such as 17-ketosteroid excretion, 17-hydroxycorticosteroid level in blood, serum electrolytes and blood studies cannot always be relied upon for diagnosis. If adrenal tumour is present, X-ray may provide valuable evidence. The authors recommend for treatment unilateral adrenalectomy with pituitary irradiation but the results are not uniformly good.

Skrimshire<sup>4</sup> observed a remission after radiotherapy over the pituitary in 4 out of 6 cases of the syndrome and recommended this form of treatment initially before surgery is contemplated. Before the advent of cortisone Sprague<sup>5</sup> inunciated the treatment of partial adrenalectomy (one adrenal totally removed and 90 per cent of the other adrenal ablated) on the basis of result of treatment in 58 cases. Bishop et al<sup>6</sup> have suggested from the experience of patients who, having undergone the operation of radical subtotal adrenalectomy, are relapsing to the extent of needing another operation, that, with increasing assurance for adequate substitution therapy, total bilateral adrenalectomy alone may provide the best treatment for Cushing's syndrome.

*Aldosterone and Primary Aldosteronism* : Simpson and Tait<sup>7</sup> reported the discovery of aldosterone in 1952 from the active amorphous fraction of the adrenal cortex. Its formula and synthesis have now been achieved. Aldosterone has been found to be 50 to 120 times as potent as D.O.C.A. in controlling the excretion of sodium and potassium in urine. The mechanism of controlling the secretion of aldosterone is not yet clearly understood. It appears that unlike other major corticoids, aldosterone is not under the complete and direct control of corticotrophin. Gordon et al<sup>8</sup> and Luetscher and Axelvad<sup>9</sup> have found that patients with hypopituitarism excrete normal quantities of aldosterone; secretion of other corticoids in hypopituitarism is however greatly reduced. Farrell et al<sup>10</sup> have shown that administration of 100 mg of cortisone or hydrocortisone daily for 5 weeks to dogs does not reduce the amount of aldosterone in adrenal venous blood though the secretion of other steroids is greatly reduced. As a result of this treatment, the adrenals underwent atrophy but the zona glomerulosa, the probable site for production of aldosterone, remained unaffected.

The syndrome of primary aldosteronism was described by Conn<sup>11</sup> in 1955. Since then many cases have been reported in the literature and Conn<sup>12</sup> has received information of more than 30 additional cases. The syndrome is caused by tumour of the adrenal cortex though in a few instances it has been found to be caused by hyperplasia of adrenal cortex.

The principal features of the syndrome are polyuria, muscular weakness, intermittent tetany, hypertension, high titre of aldosterone-like material in the urine, low plasma potassium and high sodium and alkalosis. There is no oedema. The excretion of 17-hydroxycorticoids was normal or only slightly increased. Conn suggests that many cases of potassium-losing nephritis may in reality be cases of primary aldosteronism.

*Amphenone and Suppression of Adrenal Cortex:* In recent years it has been discovered that amphenone, a diphenyl compound, synthesized by Allen and Corwin<sup>13</sup> in 1950, can suppress or interfere with corticoid synthesis by adrenal cortex. Thorn and his colleagues<sup>14</sup> studied the effects of amphenone in a patient with Cushing's syndrome due to adrenocortical carcinoma and found that the levels of 17-hydroxycorticoid in the plasma and its output in the urine were strikingly reduced, glycosuria was almost abolished, blood sugar level came down and insulin was not required.

Hortz et al<sup>15</sup> have studied the effects of amphenone in 24 patients suffering from several diseases including cancer of the breast and cervix, hyperthyroidism and adrenal hyperplasia and carcinoma. In two of these patients dying from carcinomatosis, the adrenal glands at necropsy were found remarkably enlarged and the histological picture of the cortex was similar to that found in patients who have been treated for long with corticotrophin. This enlargement may be due to accumulation of corticoid precursors, due to imperfect synthesis of the corticoids leaving the uninhibited pituitary to cause enlargement of adrenals, without increased secretion. The administration of amphenone resulted in fall in output of 17-hydroxycorticoid in one patient with adrenal hyperplasia, in one patient with adrenocortical carcinoma and in 5 out of 11 other patients with malignant disease or thyroid disorder. In 5 patients treated with amphenone, the response of steroid output with corticotrophin was inhibited. The uptake of I<sup>131</sup> by the thyroid was reduced in 7 out of 8 cases. Amphenone was not found to cause a marked reduction in the urinary output of 17-ketosteroid. Undesirable side-effects consisting of drowsiness, prostration, sweating, fall of blood pressure, gastro-intestinal disturbances, peripheral vasoconstriction, impaired liver function, skin rash and mental disturbances are commonly met with and may bar its wide use in treatment.

*Adrenal Cortex in Hypertension:* In order to find the relation between blood pressure and adrenal glands, Dawson<sup>16</sup> has studied the detailed morbid anatomy of adrenal glands in essential and renal hypertension as well as in normotensive individuals. The average combined weight of adrenal glands was 15.3 g in 90 cases of essential hypertension studied, 15.7 g in 44 cases of renal hypertension and 11.8 g in 90 cases of normotensive individuals. The enlargement was due to hyperplasia of zona fasciculata associated with irregular arrangement of cells which were hypertrophied and vacuolated and contained abundant lipid. The difference between essential and renal hypertension was noticed mainly in zona reticularis and this was more quantitative than qualitative in nature. No affection of zona glomerulosa was noted in either form of hypertension.

Dawson suggests that the changes in adrenal cortex in hypertension are secondary in nature since it is difficult to conceive a primary adrenal change in renal hypertension.

*Addisonian Crisis due to Pellagra:* Rosenthal and Less<sup>17</sup> have reported detailed studies of a female patient with pellagra in which electrolyte and steroid estimations were made during an acute phase of her illness resembling addisonian crisis. The clinical and biochemical features suggested an acute failure of mineralo-corticoid metabolism. The patient appeared to have selective damage to the zona glomerulosa which is considered to be the main secretor zone of mineralo-corticoids as suggested by Landing<sup>18</sup>.

The authors reviewed the literature on the subject and found that necropsy studies of adrenal glands in cases of pellagra have shown partial or even complete atrophy of zona glomerulosa as the outstanding feature. Variable loss of lipid and sclerosis of the capsule have also been reported but it is a striking feature that zona fasciculata and zona reticularis have remained virtually unaffected.

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## ADRENAL MEDULLA

*B. B. Mukherji*

**Phaeochromocytoma:** At the meeting of the British Medical Association, Rosenheim<sup>1</sup> has reviewed the clinical picture of phaeochromocytoma and the special methods for its diagnosis. He said it was a tumour of the chromaffin tissue most commonly found in the adrenal medulla but occasionally in the para-aortic glands of Zuckerkindl. It is usually single and benign, commonly affecting the right suprarenal but may also occur ectopically. Ten per cent of tumours are extra-adrenal, 10 per cent malignant and in 10 per cent of cases the tumour is bilateral. The classical picture of paroxysmal hypertension in an usually normotensive subject, accompanied by blanching of skin, palpitation and throbbing headache was not commonly seen. The established condition closely resembled essential hypertension. The clinical picture varied from patient to patient depending on the relative amounts of adrenaline and noradrenaline secreted by the tumour. Two symptoms of particular importance were intense cutaneous vasoconstriction and profuse sweating. The diagnosis could be confirmed by: (1) Pharmacological tests on the patient. Attacks of hypertension could be provoked by histamine though occasionally false negative results are obtained. Alternatively, hypertension might be relieved by use of hypotensive drugs of which phentolamine was the most effective. False positive results with phentolamine were obtained if the patient had barbiturates or was anaemic. (2) Assay of blood and urine for pressor amines. (3) Once diagnosed, the tumour could sometimes be located by presacral oxygen insufflation followed by tomography.

Burn and Field<sup>2</sup> have devised a colorimetric method for the diagnosis of phaeochromocytoma. This test depends on a colour reaction given by catecholamines in the urine. The authors diagnosed two cases by this method which were subsequently confirmed. They recommend it as a screening test, the positive results being subjected to biological assay for confirmation.

Weil-Malherbe<sup>3</sup> has reported a case of phaeochromocytoma in which the urinary excretion of 3-hydroxytyramine was increased as much as, or more than, the excretion of noradrenaline. After surgical removal, the tumour was found to contain, in addition to adrenaline and noradrenaline, large quantities of 3-hydroxytyramine and 3:4-hydroxyphenylalanine (DOPA). Litchfield and Peart<sup>4</sup> have reported a case of phaeochromocytoma (which was subsequently removed by operation) which had a normal urinary excretion of adrenaline and noradrenaline even during typical attacks. Gjøl et al<sup>5</sup> have reported a case of phaeochromocytoma in which the patient on two occasions had a severe shock following the hypertensive crisis and the shock was successfully treated with l-noradrenaline. The authors recommend that noradrenaline should be tried in such emergencies. Beard et al<sup>6</sup> reported a case in which a normotensive blood pressure was maintained immediately after the operation by intravenous infusion of 128 mg of noradrenaline over a period of 15 hours and then the patient suddenly collapsed and died presumably from ventricular fibrillation. The authors wonder if slight oxygen deprivation during anaesthesia has made the myocardium susceptible to noradrenaline and recommend the use of quinidine when such large doses of noradrenaline are needed.

Drukker et al<sup>7</sup> have reported a case of hyperplasia of adrenal medulla which gave rise to a clinical picture closely resembling that of phaeochromocytoma. The left adrenal was removed without any effect. After removal of the second adrenal the symptoms and most of the signs disappeared and the improvement was maintained for 5 months. Mason et al<sup>8</sup> have reported an infant having attacks of paroxysmal hypertension due to release of adrenaline and noradrenaline from a large intrathoracic tumour. The tumour was successfully removed and proved to be not a phaeochromocytoma but a histologically malignant neuroblastoma containing adrenaline and noradrenaline.

Von Euler et al<sup>9</sup> have described a method of localizing pheochromocytoma which they found useful in one case. This was done by catheterizing the inferior vena cava and estimating noradrenaline in samples collected at different levels.

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## ADRENOCORTICAL INFLUENCE ON SKELETAL MUSCLE—See SKELETAL MUSCLE, ADRENOCORTICAL INFLUENCE ON

## ALCOHOLISM

W. R. Bett

**Antabuse** : Pfeffer and his colleagues find antabuse (Disulfiram) useful in alcoholism, when given in conjunction with psychotherapy. In their experience there are few absolute contra-indications to its use. Borderline psychosis is, in general, a contra-indication but, if special circumstances warrant it, minimal doses should be administered. Mild side-effects such as drowsiness or headache are minimized by giving small doses of the drug.

**Citrated Calcium Carbimide** : Bell treated 64 patients over a four-month period with citrated calcium carbimide, 50 mg daily by mouth, as a substitute for antabuse ; 26 of these patients had previously been given antabuse, and side-effects had occurred in 23. Citrated calcium carbimide caused no side-reactions, and the protection which it afforded was ' instantaneous '. In contrast to antabuse, there is no carry-over period of protection on cessation of treatment.

**Reserpine** : Reserpine (Serpasil), which has been used as a tranquillizer in the treatment of various neurological disorders and of hypertension, was tested by Avol and Vogel for its effect on 23 patients with delirium tremens. Given parenterally in doses ranging from 2.5 to 5 mg, it freed the majority of these from symptoms of acute hallucinations in an average of 18 hours. Because of the great variation in reaction to the drug, the authors recommend that dosage should be adapted to individual needs. An initial dose of 2.5 mg followed by a second dose in three hours, if required, was considered safe for all patients. Although relatively high doses were used in this series, no ill-effects were observed. The period of recovery from post-alcoholic withdrawal symptoms was considerably shortened.

Greenfield's experience with 55 acutely intoxicated chronic alcoholics provides further indication that the sedative and anxiety-relieving properties of reserpine may be valuable in the long-term treatment of chronic alcoholism. A good response was obtained in 51 patients. Reduction in the incidence of post-alcoholic ' jitters ' is described as one of the chief advantages of this treatment, since it is these ' jitters ' which are frequently the cause of the patient's return to alcohol or of addiction to drugs.

**Promazine** : Promazine (Sparine), a derivative of phenothiazine, was administered by Mitchell in doses of 25–100 mg orally every 4–6 hours to 141 patients with acute alcoholic intoxication. The course lasted 3–5 days. All the patients who completed the treatment (97 per cent) were relieved of their withdrawal symptoms. Nausea and vomiting were quickly controlled in 89 per cent, and fluids and food could be taken immediately after treatment was begun. The only adverse reactions noted were dizziness and postural hypotension. Given intramuscularly, the drug caused little pain or local tissue reaction.

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## Alcohol Poisoning, Medicolegal Aspects of

### ALCOHOL POISONING, MEDICOLEGAL ASPECTS OF

D. Bhaskara Reddy

Cases of mild or medium intoxication are chiefly of medicolegal interest. The more severe states of intoxication are a problem to the casualty staff and present themselves as emergencies. They are liable to a variety of complications. The time taken to reach the various stages in alcohol intoxication depends upon the individual susceptibility, habituation, amount of drink taken and the concentration of alcohol, the speed of ingestion and the presence of circumstances promoting absorption. There is still no conclusive clinical test to determine the degree of alcoholic intoxication. Walter (1954)<sup>2</sup> has recorded the significance of positional nystagmus in cases of alcohol intoxication which occurs constantly after the consumption of a critical amount of alcohol which although varying with individual tolerance has a maximum value equivalent to 60 c.cm of absolute alcohol. This phenomenon cannot be suppressed by voluntary effort especially if the subject is provided with +12D lenses to prevent fixation and its presence always indicates that the individual's alcohol tolerance has been exceeded. This type of nystagmus occurs in three stages: (1) This is seen with the subject lying on one side when a lateral nystagmus occurs, the quick component of which is directed towards the side on which the patient is lying. The direction is reversed when the subject turns over. The stage occurs about 79 ± 43 minutes after he started to drink and lasts for 216 ± 50 minutes after drinking ceases; (2) The neutral period during which no nystagmus is observed follows next and lasts 35 ± 19 minutes; (3) This consists of a positional nystagmus in the reverse direction, that is with the quick component directed away from the side on which the subject is lying. This appears some 4 to 5 hours after drinking has ceased and gradually subsides over a period of 10 to 16 hours. These three stages are not correlated exactly in reference to blood alcohol curves but the first stage usually begins when the concentration of alcohol in the blood has reached 0.06 per cent. Blood alcohol determination and testing for the presence of positional nystagmus, together give very reliable objective means of estimating the degree of intoxication and incapacity.

**Methyl Alcohol Poisoning :** Poisoning by methyl alcohol is uncommon and usually occurs in minor outbreaks. Methyl alcohol is used commercially as a solvent for paints, varnishes and shellacs and is present in some antifreeze mixtures. Sometimes alcoholic beverages, e.g. whisky is administered with methyl alcohol. MacDougall and MacAulay (1956)<sup>1</sup> have given a clear account of 60 cases of addiction to methylated spirit between March 1950 and July 1955. Only one of the addicts was a woman whereas 549 addicts of alcohol included 30 females. Originally all these persons drank the commoner beverages but turned to methylated spirit and its compounds for economy. They all showed group characteristics of emotional blunting, a tendency to vagrancy, pessimism and depression but were not actively psychotic and responded to treatment equally as well as other addicts, sometimes even better. Methylated spirit is less dangerous to life than is often supposed. MacDougall and MacAulay (1956)<sup>1</sup> never found specific lesions of poisoning such as optic neuritis or atrophy in any one of these cases. The findings were the same as in the case of prolonged overdosage of ethyl alcohol.

**Treatment** consists of detoxication and sedation followed by administration of vitamins B complex with C and potassium bromide 60 gr twice a day. This could be augmented by psychotherapy and group therapy.

In cases of ethyl alcohol poisoning vitamin B<sub>6</sub> in 100 mg doses intravenously has been shown to be of considerable value which acts by detoxicating (by promoting the metabolism of) alcohol.

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### ALIMENTARY INTOXICATION—See HEPATIC COMA AND ALIMENTARY INTOXICATION

### ALIMENTARY PHYSIOLOGY

J. C. Sachdev

**Salivary Secretion :** Schaeyer and Levin<sup>132</sup> found that submaxillary glands contribute about 69 per cent, parotid glands 26 per cent and the sublingual glands 5 per cent of the total secretion

of saliva. White et al<sup>149</sup> found Na to be  $26.4 \pm 11.8$ , K  $19.7 \pm 39$  and Cl  $29.0 \pm 8.8$  mEq/L in 73 normal subjects in the fasting state after chewing paraffin.

Coats et al<sup>17,18</sup> demonstrated that parasympathetic stimulation augments sheep's continuous salivary secretion but sympathetic stimulation causes only a transient increase followed by a fall. They also observed that after an initial establishment phase of 1-2 minutes' duration following parotid nerve stimulation, an increasing salivary flow was associated with an increase in the concentration of sodium and bicarbonate and a corresponding decrease in the concentration of potassium and phosphate. Denton<sup>24</sup> demonstrated that the daily volume and sodium content of saliva decreases and potassium content rises if the sodium replacement is not adequate. On transfer of potassium from salivary cells, saliva is increased initially on parasympathetic stimulation in dogs.

Small amounts of plasminogen activator and large amounts of plasminogen proactivators, but neither plasminogen nor trypsin inhibitors are found in human saliva<sup>9</sup>. Salivary plasminogen is more plentiful when the glands are not stimulated and thus the plugging of the ducts, when the flow is least vigorous, is prevented<sup>1</sup>.

Glucose-6-phosphate dehydrogenase values were higher in rats when their salivary glands were irradiated while the rest of the animal was shielded. No significant difference was noticed for isocitric acid dehydrogenase under similar conditions<sup>38</sup>.

**Denervation Sensitivity:** Sympathetic denervation renders the submaxillary gland more sensitive to the secretory action of acetyl choline, epinephrine and pilocarpine. A greater sensitization was found for acetyl choline and pilocarpine after post-ganglionic than after preganglionic denervation<sup>8</sup>. It has been found that in the denervated gland pilocarpine prevents the usual fall in cholinesterase and amine-oxidase and also the supersensitivity to acetyl choline, epinephrine and norepinephrine<sup>125, 126</sup>. Existence of apparently more than one mechanism involved in denervation sensitivity has been pointed out<sup>127</sup>.

**Relation to Thyroid:** Relation of salivary iodide to protein-bound iodide is an index of thyroid function<sup>12</sup>. Some destruction of thyroid hormone probably takes place in salivary glands<sup>151</sup>. Salivariectomy does not interfere with the salivary uptake of  $I^{131}$  in human beings<sup>14</sup> and in rats it does not effect their thyroid status<sup>104</sup>.

**Gastric Secretion.—Composition and Secretion:** Kirsner et al<sup>82</sup> reported that the morning basal (fasting) gastric secretion, varies greatly among individuals; the volume of secretion and concentration of hydrochloric acid may fluctuate independently. They further found that the basal secretion varies in the same person at different times but the level of secretion (high, medium or low) tends to be reproducible in a pattern consistent for the individual. Present knowledge regarding the protective function of mucin has been reviewed by Florey<sup>45</sup>. He has also tried to demonstrate metabolic differences in the mucus secreting cells in the different parts of the stomach<sup>71</sup>. The variations in pattern between individuals exceed those for the same individual. Ivy et al<sup>69</sup> studied gastric secretory response to various amounts of food and found that there was an optimum secretory response with an optimum-sized meal in Heidenhain's pouch in dogs.

A circumscribed region in the anterior part of sigmoid gyrus on electric stimulation inhibits motor gastric function but it augments the secretion of HCl<sup>36, 62, 77</sup>.

Richmond et al<sup>114</sup> fractionated the nondialysable components of human gastric juice and found that all the carbohydrate does not exist as mucoprotein and that these fractions were biologically active in some respects. Dragstedt et al<sup>29</sup> have reviewed the physiological mechanism of the gastric antrum.

It has been revealed that in dogs vagal stimulation of gastric acid secretion is mediated mainly by direct cholinergic action on fundic glands<sup>106</sup>.

Imparato et al<sup>68</sup> investigated gastric secretion in response to insulin hypoglycaemia and electrical stimulation of the vagus nerve in dogs who had bilateral vagosplanchnic anastomosis and came to the conclusion that there are preganglionic fibres in the greater splanchnic nerve whose relationship to gastric secretory apparatus is similar to that of cholinergic fibres in the vagus.

Babkin has pointed out the relationship between carbon dioxide tension and gastric secretion<sup>8</sup>. Waddell observed that antrectomy diminished the stimulatory effects of histamine and vagal impulses and has suggested that gastrin exerts a tonic effect upon central nervous origins of the vagus nerve but it seems possible that the site of the tonic effects was the stomach itself<sup>147</sup>.

## Alimentary Physiology

Increase in the volume of the gastric secretion, the free and total acidity and in the pepsin content resulted on stimulation of preoptic and medial parts of the anterior hypothalamic region, the amygdaloid group of nuclei, the tip of the temporal lobe and the orbital surface of the frontal lobe<sup>134, 135</sup>.

Kochhar<sup>81</sup> has reviewed the biochemistry of gastric disorders. He discusses the importance of fractional gastric analysis, with particular reference to achlorhydria, hyperacidity, carcinoma and pyloric obstruction.

Pathak and Pai<sup>110, 111</sup> have reported their observations on the gastric response—digestion and evacuation time, to some of the common Indian preparations, both vegetarian and non-vegetarian. These workers believe that pyloric evacuation and consistency in the size of the particles seem to be the important determining factors.

Recently the results of fractional gastric analysis in 50 healthy subjects have been reported by the same authors.

*Effect of Hormones, Vitamins and Emotions on Gastric Secretion* : Villarreal et al<sup>144</sup> demonstrated a hormonal mechanism for gastric secretion mediated through the adrenal gland and independent of the vagus nerve.

Lahiri<sup>89, 90</sup> observed that desoxycorticosterone diminished the quantity of the gastric secretion along with quantitative diminution of the total gastric chloride, but caused an increase of the plasma chloride in the majority of their cases. Succinic dehydrogenase concentration increased in rats, mice and guinea pigs, after injection of ACTH, pilocarpine, neostigmine and caffeine. Alcohol however, had no influence, nor did atropine and scopolamine, the effects of histamine and insulin were equivocal<sup>139</sup>. These workers further undertook a comparative study of the actions of desoxycorticosterone on gastric and urinary secretion of water and chloride and reported more marked decrease in water and chlorides of gastric juice than similar effects on the volume and chloride content of the urine. Hyperchlorhydria has been found in patients with Cushing's syndrome<sup>78</sup>.

Vitamin D was found to increase the volume and acidity of the gastric secretion after the feeding of rachitogenic diets and this could be correlated with increase in serum phosphorus<sup>60</sup>.

Acid secretion increases during the first half and decreases during the last half of menstrual cycle while pepsin and chloride secretions are not altered<sup>93</sup>.

*Effect of Drugs on Gastric Secretion* : Ethyl alcohol stimulates the secretion of acid and the volume of gastric juice ; histalog, and butazolidine<sup>79</sup> increase gastric acidity. The authors have discussed the mechanism of action of these drugs<sup>59, 148</sup>.

Reserpine causes an increase of the acid secretion which is mitigated by atropine, banthine or by epinephrine but these effects are not seen in doses used therapeutically<sup>122, 113</sup>.

Histamine in small doses in pyloric-ligated rats caused an increase in the volume and H-ion concentration and in large doses the incidence of severe ulceration was doubled<sup>76</sup>.

Ivy et al found increased gastric secretion by injecting histaminase inhibitors Marsilid and Rimifon in dogs, in doses which would neither reduce blood pressure nor would be toxic<sup>67</sup>.

The authors have studied the inhibitory effect of atropine on histamine-stimulated gastric secretion in dogs and have reviewed briefly the possible alternative formulations of the role of acetyl choline and histamine, in stimulating the parietal cells. Histamine is probably the long-acting final common chemical pathway for all stimuli to the acid-secreting cells<sup>70</sup>.

Berkowitz<sup>6</sup> observed achlorhydria in most cases with peptic ulcer after administration of *spansule*, a preparation of belladonna alkaloids and for an average ulcer patient a dose of 0.8 mg administered every eight hours was found to be satisfactory.

Shayer et al<sup>120</sup> reported that C<sup>14</sup> histidine injected subcutaneously in chronic fistula rats led to the release of C<sup>14</sup> histamine on feeding, which caused gastric secretion when amino-guanidine was present to prevent histamine destruction.

It has been pointed out that accumulation of yttrium in various tissues of dogs and rabbits is probably related to the pH and therefore it might be helpful in the study of acid secretion<sup>28</sup>.

*Effect of Enzymes on Gastric Secretion* : Elevation in uropepsin was produced by injections of hydrocortisone but not with cortisone<sup>145</sup>. Similarly not much difference was observed in the output after cortisone by Necheles<sup>102</sup>.

Low uropepsin output was observed in pernicious anaemia, hypofunction of the adrenals or the pituitary, myxoedema, total gastrectomy and gastric cancer<sup>55</sup>.



Vitale et al<sup>143</sup> have concluded from their studies in guinea pigs and human subjects that succinic oxidase may be involved in production or secretion of hydrochloric acid. This role of succinic oxidase has also been studied by Davenport et al<sup>25</sup>. These workers have also demonstrated the inhibitory effect of iodoacetic acid and N-ethyl maleniamide which attacks sulphhydryl groups in the mouse<sup>26,27</sup>.

Rigler et al<sup>118</sup> could not find any correlation between uropepsin and either gastric acid or gastric pepsin secretion.

A linear relationship was found between the dose of histamine and plasma pepsinogen. Antihistaminic or sodium pentobarbital could not annul this effect<sup>80</sup>.

Existence of an inhibitory mechanism localized to the duodenum has been strongly pointed out<sup>7</sup>.

Uropepsin excretion tends to be higher in males than in females, higher after adolescence than before and to diminish somewhat in man after the age of 60<sup>10</sup>. Bauer<sup>11</sup> and Spiro<sup>133</sup> observed that uropepsin and blood pepsin are influenced by the renal function; uraemia lowers uropepsin but raises blood pepsin, which is also higher in patients with duodenal ulcer and lower after gastrectomy<sup>119</sup>. Testosterone administration increases uropepsin output in normal males especially in older men<sup>9</sup>.

Inhibitory effect on gastric hydrochloric acid (without alteration in total volume) has been shown after administration of diamox, pro-banthine and pathilon and they support the concept that carbonic anhydrase in the parietal cells has an important role in the process of acid secretion of the stomach<sup>138</sup>.

Stern<sup>121</sup> suggested that the muscular effects of histamine depend upon its union with diamine oxidase which is found in the muscular parts of the rabbit stomach, but not in the mucosa. Antihistaminic drugs prevent this reaction in the muscle of the stomach only.

Stomach distended by introduction of water or a balloon 20 to 40 minutes prior to intravenous injection of 20 per cent sodium chloride, caused inhibition to the drinking response usually after injection, which was abolished by cocainization<sup>94</sup>.

**Gastro-intestinal Motility:** One cross-sectional area near the ampulla of Vater in bitches serves as a pace-maker for slow electrical waves that appear to control or accompany rhythmic movements in the intestine and the factors influencing the pace-maker and its influence on jejunum have been discussed<sup>95,2</sup>.

Parasympathetic stimulation caused contraction of rabbit colon while sympathetic stimulation caused relaxation. Intensity of effects depended upon the frequency of electrical impulse. Simultaneous stimulation of both sets of nerves, at low frequency only, caused contraction<sup>49</sup>.

Valvular action of the ileocaecal valve has been observed through a sigmoidoscope in a patient with caecostomy<sup>140</sup>.

Lorber et al<sup>87</sup> by recording changes in gastric, antral and duodenal cap motor activity and continuous recording of intraluminal pressures in these areas found in most of the instances a co-ordination of motor activity in the duodenal cap area.

It has been suggested that colonic activity should be classified into three wave types, incoordinated phasic, tonic, and propulsive. The last is preceded by abolition of the first two<sup>30,31,32</sup>.

Kirsh<sup>74</sup> reviewed the Roentgen examination of small intestine using a nonflocculating medium and found that the time of transit was shorter if small amount of sodium carboxymethyl cellulose was added to barium sulphate suspension.

A satisfactory method for measuring the volume of gas in the gastro-intestinal tract by plethysmographic application of Boyle's law has been presented by Bedell et al<sup>4</sup>. Farrar and Ingelfinger<sup>41</sup> demonstrated the feasibility of estimating gastro-intestinal motility by auscultation.

Excretion time for five per cent of dye marker fed with oats to goats was fairly constant but the 95 per cent excretion time showed considerable variability<sup>20</sup>.

**Effect of Hormones, Vitamins, Drugs and Enzymes etc. on Gastro-intestinal Motility:** Streeten et al<sup>128</sup> found that adrenal cortical extract in low concentration only or aldosterone in amounts contained in these extracts increase the peristaltic contractions of the small intestine, ability to propel fluid against pressure gradient and restore the fatigued intestinal segment to normal peristaltic activity, and in high concentration on the other hand, they inhibit or abolish the peristalsis. Possibility of the role of aldosterone in controlling intestinal motility has been pointed out.



## Alimentary Physiology

Daniel et al<sup>33</sup> found diminished gastro-intestinal propulsion following potassium deficiency accompanied by sodium restriction, while, administration of cortisone or depletion of electrolyte by intraperitoneal sucrose solution decreased propulsion but did not cause depletion of intestinal potassium, though cortisone caused severe hypocalcaemia.

The Ca-P ratio was of importance in absorption of calcium from the duodenum of rachitic chick receiving vitamin D and it caused increased Ca absorption while in normals it was of no importance in calcium absorption. Increased peristalsis was obtained when vitamin D or 1 : 1 Ca : P-containing food was given<sup>48</sup>.

Comparative effects of pamine, banthine and placebos were studied on gastro-intestinal motility. It was observed that pamine and banthine each given orally can bring about the delay in forward movement of barium along the intestine and only banthine caused a significant delay in the evacuation of barium from the stomach<sup>22</sup>.

X-ray irradiation of the whole body led to decrease in plasma and intestinal cholinesterase in rats and guinea pigs but not in monkeys under the conditions of the experiments while peristaltic responses of the monkey and guinea pig intestinal loops to intraluminal pressure were normal<sup>44</sup>.

**Gastro-intestinal Absorption:** Benson et al<sup>13</sup> concluded that optimum absorption of olive oil occurs in the third quarter of the small intestine of the rat and within experimental limits this capacity is neither dependent upon the duration of the period of absorption nor upon the autonomic proximity of this area to stomach.

Absence of pancreatic juice or both bile and pancreatic juice, considerably decreased the total fatty acid output in the thoracic duct lymph in dogs<sup>75</sup>.

It is suggested that phosphorylation and dephosphorylation are functional steps in the absorption of fructose from the alimentary tract of rat<sup>107</sup>.

Fat absorption studies in normal, ethionine-administered and alloxan-diabetic rats for periods of 2, 4 and 6 hours revealed that the absorption was reduced for 2 and 4 hours period in ethionine-administered animals and in uncontrolled diabetic rats there was a decrease in the absorption in 2 hours period only<sup>129</sup>.

It has been observed that oils and fats and their glyceride fractions are completely digestible in rats, and it has been suggested that it is the melting point rather than the glyceride structure of the fats which controls the digestibility of fats<sup>103</sup>.

It is suggested from observations made after intragastric administration of sodium taurocholate, oleic acid or cholesterol, that essentially all the cholesterol transferred from the intestinal lumen to the lacteals is esterified<sup>142, 92</sup>.

Higgins et al<sup>57</sup> inhibited the motor activity of the small intestine by injection of banthine and found that the rate of absorption in such a group was reduced when compared with those of fasted healthy persons.

Glass et al<sup>50, 52</sup> have demonstrated complete block to the absorption of vitamin B<sub>12</sub> in conditions of pernicious anaemia, both in relapse and remission, after total gastrectomy and in sprue; and have reported the methods by which this block can be overcome. Recently the methods of measuring isotopic vitamin B<sub>12</sub> absorption by the radioactive cobalt content of urine, faeces and liver have been widely explored. Vitamin B<sub>12</sub> absorption is deficient in pernicious anaemia, after gastrectomy, sprue and in conditions of small bowel that promote the growth of abnormal flora, and also to a slight extent in older people with hypochlorhydria<sup>37, 58, 64, 83, 117, 136</sup>.

Herting et al<sup>61</sup> studied the absorption of acetic acid and glycerol from pylorous-ligated rat stomach. In six hours, acetic acid showed a log-dose response, with 2.0 mm being absorbed at the highest level administered, under the same conditions glycerol absorbed reached and maintained a constant level approximating to 0.4 mm.

l-isomers of histidine, phenylalanine, alanine and glycine have been demonstrated to be actively absorbed in perfused guinea-pig gut but not their d-isomers nor the l-forms of glutamic and aspartic acids<sup>43</sup>.

Simmonds<sup>124</sup> and Tasker<sup>137</sup> found that protein or carbohydrate feeding did not change rats' thoracic duct lymph.

Potassium inhibits absorption of both sodium and glucose from rats' small bowel but has no such effect on the colon<sup>16</sup>. It has been confirmed that there is reciprocal effect of sodium and potassium concentrations in human ileum tending to preserve the osmolarity of the luminal contents<sup>46</sup>.

A significant percentage of total body sodium and potassium in case of rabbit was found to be present in the gastrointestinal tract<sup>40, 105</sup>.

Absorption of glucose and urea from balloon-isolated loops of human bowel revealed that these were more rapidly absorbed by the jejunum than by the ileum and more concentrated the solution was, more pronounced was the difference<sup>21</sup>.

Glucose absorption is poor in X-ray irradiated mice. This is not related to hexokinase content of the intestine<sup>34</sup>.

Rat and cat intestines have been shown by using *in vitro* studies with labelled amino acids to be capable of deamination.

In the rat's isolated small bowel, water absorption cannot occur even at pressures up to 45 c.cm of water unless glucose is also present in the lumen<sup>47</sup>.

The rate of water absorption was found to be 2.5 per cent of the administered dose per minute in stomach and 23 per cent per minute in the small bowel for isotonic or hypotonic saline. This rate was not altered by varying the saline concentration from 0 to 5.4 per cent but it diminished somewhat by hypertonic salt solution in the small bowel<sup>91</sup>.

Lepkovsky<sup>88</sup> found that withholding of water during meals in rats did not interfere with digestion but it definitely decreased appetite and effected a reduction of food intake. Water content of the intestinal lumen in all rats, irrespective of the availability of water with meals, was approximately similar.

Digestion and absorption of casein in healthy human subjects caused depression in eosinophilic count, while gelatin was without such effect and this difference has been explained due to different amino acid composition<sup>142a</sup>.

Studies on osmotic tension of cells of gastric mucosa revealed that the permeability is probably closely related to the oxygen supply and superficial gastric erosions in ischaemia have been explained on this basis<sup>100a</sup>.

Stanley et al<sup>123</sup> observed that intestinal absorption of cholesterol in patients with biliary obstruction is poor.

Rosenman and Friedman<sup>115</sup> collected thoracic duct lymph from normal and hyper- and hypothyroid rats following a test dose of cholesterol dissolved in olive oil ; but no significant alteration in intestinal absorption of cholesterol was found in disturbed thyroid function.

**Pancreas.**—The parasympathomimetic agents produced but a slight increase in the volume output of the pancreas, when given with small doses of secretin. On the other hand, with large doses of secretin, peripheral stimulation of the vagus above the diaphragm caused either a decrease or no change in the total volume output ; amylase concentration was always increased with adequate stimulus<sup>86</sup>.

It has been demonstrated that trypsin and anti-fatty liver factor are almost equally effective in preventing fatty livers in pancreatic duct-ligated rats when administered in similar quantities. Close relationship between the proteolytic enzymes and anti-fatty liver fractions of the pancreas has been pointed out<sup>130</sup>.

**Pancreatic Inhibition :** Kalser and Grossman<sup>72</sup> detected a trypsin inhibitor in pancreatic juice and it was shown that the properties of this inhibitor are similar to the crystalline trypsin prepared from pancreatic tissue by Kuntz. The duodenal mucosal extract inactivates the inhibitor. Administration of carbon tetrachloride or methionine-free diet to pregnant dogs led to the production of pancreatic exocrine deficiency, pulmonary emphysema and bronchial dilatation in the offsprings<sup>141</sup>.

Dreiling found that diamox inhibits the total volume, total bicarbonate and total enzyme secretion of the pancreatic juice. The chloride concentration varied inversely with the bicarbonate concentration<sup>23</sup>.

Guth<sup>56</sup> studied the possible correlation between the concentration of enzymes and protein nitrogen and also the possible effects of variations and found that with the exception of the relationship between amylase and protein nitrogen there was no significant effect of meals.

Komarov<sup>73</sup> did not find any evidence of consistency of ratio of proteolytic activity to protein nitrogen in the pancreatic secretion. Significant difference in the concentration of inhibitory substances was noticed in some instances.

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**Effect of Hormones and Enzymes on Secretion :** Pituitary growth hormone and the question of pancreatic secretion of 'glucagon' has been investigated by Sirek et al in dogs whose findings cast doubt on the pancreatic origin of the hyperglycaemic material<sup>131</sup>.

An increase in the specific gravity and amylase content but no change in the volume of the external secretion of pancreas was observed after the intravenous administration of hypertonic glucose solutions<sup>19</sup>.

*In vitro* studies have revealed that the lipase clears up lipaemic serum but it does not do so in the presence of fluoride or quinine<sup>66, 101</sup>.

The existence of a new porcine pancreatic enzyme 'pankrin' with proteolytic properties different from those of trypsin or chymotrypsin has been reported<sup>53, 54</sup>. Ziffren and Hosie<sup>153</sup> found a collagenase in canine pancreatic juice.

Fasting, partial pancreatectomy and parenteral ethionine, lead to decrease in serum amylase in rats. On the other hand amylase concentration is increased by a high fat diet but not by a high starch or sucrose diet which only increases the pancreatic tissue amylase<sup>150</sup>.

**Absorption :** In rat there is relatively little decrease in cholesterol absorption after pancreatectomy<sup>3</sup>.

In the presence of pancreatic damage if more iron is fed to rats the more is absorbed<sup>84</sup>.

Bile and pancreatic juice given together only restore normal cholesterol absorption in pancreatic and bile duct-ligated animals<sup>65a</sup>.

It has been found that exclusion of the pancreatic juice, significantly decreased the utilization of saturated and unsaturated fats, but it did not influence their absorption<sup>85</sup>.

**Appetite and Hunger :** Bilateral electrical destruction of the lateral hypothalamus produced aphagia and destruction of the ventromedial nucleus led to hyperphagia in cats and monkeys<sup>2a</sup>. Stimulation of the lateral hypothalamus at the level of the dorsomedian nucleus produced violent drinking movements in rats<sup>51</sup>.

The feeding of proteins created a reciprocal relationship between the serum amino acid concentration and appetite in human volunteers. An attempt to relate appetite to the major essential nutrient, i.e., proteins, has been made. The amino acid pattern of extracellular fluids, modified by the intestine and liver are assumed to interfere with the desire for food. One may refer to the original articles for details<sup>97, 98, 99, 100, 108, 109, 116</sup>.

It has been pointed out that the stretch receptors in the stomach probably constitute the peripheral mechanism for the immediate satiation of hunger and thirst<sup>112a</sup>.

Mayer<sup>96</sup> believes that appetite is regulated by a centre in the brain sensitive to glucose utilization and that peripheral arteriovenous sugar difference is a good index of satiety. This observation is supported by Stunkard et al<sup>136a</sup> that injections of glucagon could abolish hunger contractions.

An editorial in the *Lancet* has discussed the general field of appetite and it has also been discussed by Yudkin<sup>132</sup> who believes that monotony or satiety insures variety in food choice<sup>39, 65</sup>.

The present status of our knowledge regarding appetite has been beautifully dealt with in a symposium organized by the New York Academy of Sciences<sup>65</sup>.

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## ALKAPTONURIA AND PHENYLKETONURIA

J. B. Mehta

Very few cases of *alkaptonuria* have been described in India. So far only five reports have appeared in Indian journals, two of which were reported in the last two years. (Mehta and Kasliwal, Sarin and Bhargava)<sup>7,9</sup>. Some of the recent advances are outlined in the former publication.

Tyrosine excretion in premature babies superficially resembles *alkaptonuria* in that in *alkaptonuria* tyrosine and phenylalanine are incompletely oxidised and the amount of homogentisic acid in the urine is proportionate to the tyrosine in the diet<sup>7,8</sup>. In premature infants tyrosine is excreted in the urine if the diet is high in protein and vitamin C-free, but not if vitamin C is added<sup>5</sup>. This suggested a line of treatment for *alkaptonuria*, but vitamin C administration, even in 500 mg dose daily, proved of no benefit<sup>7</sup>. The value of cortisone and ACTH is still doubtful. Cope and Kassander reported good results in *ochronosis* but Biggs and Cannon reported otherwise<sup>1,3</sup>.

*Phenylketonuria* is an allied metabolic disorder, phenylalanine being the toxic amino acid whose metabolism is blocked. The importance of this condition is in the fact that it is associated with mental deficiency in contrast to *alkaptonuria* which is a relatively harmless metabolic disorder. Woolf et al have shown that the mental deficiency is directly related to phenylalanine accumulation in the body. They treated three such cases on an artificial diet devoid of phenylalanine but adding tyrosine and tryptophane artificially. Definite improvement of mental faculty resulted in all the three cases<sup>4,10</sup>. The diet consisted of specially prepared casein hydrolysate from which phenylalanine had been removed, wheat starch (free of protein), little milk, salts, vitamins and other essential amino acids. Growth was well maintained and nutritional deficiency was not noted. The chief disadvantage of this diet is the rather high cost and special preparation.

Phenylketonuria with normal intelligence has been reported. Two such recent reports are published<sup>2,6</sup>. The normal colour of the hair in these cases and a lowered excretion of phenylpyruvic acid and phenyllactic acid are suggestive points for speculation. The rest of the biochemical examination including phenylalanine excretion is as in mentally defective phenylketonuria. Coates' case presented as a case of muscular dystrophy<sup>2</sup>.

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### ALLERGY

R. M. Kasliwal and J. P. Sethi

In the past few years, such a considerable amount of work has been done in the field of allergy and immunology that it is difficult to cover all such in this article. However, an attempt has been made to explain the present day concept of allergy.

Although hypersensitivity has been known since antiquity, the more precise term allergy was coined by von Pirquet in 1906, to connote the altered reactivity that results from contact with such diverse substances as tubercle bacilli, toxins, immune sera, etc. von Pirquet's definition included both hypersensitivity and hyposensitivity. In 1907, Coca used the term atopy to signify allergic disorders with a familial background and regarded hay fever, bronchial asthma and atopic dermatitis as the atopic diseases. Many authors now use the term allergy to include all forms of hypersensitivity. The general concept however, is that allergy is altered reactivity on the part of an organism resulting from exposure to the reactant or the allergen, excluding those reactions which are known to be due to the pharmacodynamic, toxic or the cumulative effects of the particular allergen.

*Fundamental Status Allergicus* : The problem of fundamental status allergicus still remains unsolved. Basic factors operative in the production of antibody and the reaction of it with the antigen in the experimental work and the spontaneous sensitization of man remain unanswered. For the allergic state, Rackeman used the simile of a loaded gun ; the patient bears a charge which is quite unnoticed until one or the other of a wide variety of trigger mechanisms sets it off. The fundamental question then is, why is the patient loaded, why is he different from his non-sensitive fellows and how does he acquire such a state ? Comparatively little is known about such a basic allergic state. There is reason to believe that a solution lies in finding out the nature of the basic constitution. At present the only information concerning the constitutional factor in allergy is that it is usually inherited, although even that fact is questioned by some. In the presence of hereditary or other constitutional tendencies hitherto unknown, the individual may become sensitized to a specific allergen. On re-exposure to a sufficient quantity of that allergen he manifests allergic symptoms.

Suggestions have been made to link allergic manifestations with certain personality types or psychogenic factors. Some authors regard that persons become allergic, since they have a certain constitutional make-up and that allergy is mostly a matter of psyche. Though not all workers believe in the existence of a predisposing personality or a psychogenic constitutional defect in allergic persons, nevertheless, it is admitted that psychogenic factors may initiate or aggravate allergic symptoms.

Hereditary factors have been considered of foremost importance. In a great majority of patients the incidence of allergy in the offspring is increased if both the parents suffer from allergic disorders. The characteristic inherited is the allergic tendency—a susceptibility to sensitisation.

A defective endocrine system has been blamed for the allergic tendency. The dramatic therapeutic results obtained with ACTH and cortisone and also the changes in bronchial asthma during pregnancy have led to the consideration whether allergic symptoms represent abnormal function of the hypophysis or of the adrenal gland. Such work has dealt usually with the excretion of ketosteroids, and with the studies on the responses to glandular stimulating or to stressing agents. The results so far are controversial and do not lead to a definite conclusion as to the adequacy or otherwise of the hormonal function in allergic individuals, in spite of the greater evidence that certain responses in the allergic individuals are altered.

*Allergic Reactions* : Hypersensitive states have been divided into two main types. 1. Immediate reactive type and 2. the delayed reactive type. Under the immediate reactive type are included, anaphylactic shock, Arthus phenomenon and atopic reactions like hay fever, asthma, serum sickness, angio-oedema, etc. The immediate states are associated with the presence of humoral antibodies. Reactions of the immediate type involve specialised tissues in the various regions of the body especially smooth muscle, vascular endothelium and collagen; moreover, there is only a brief interval between the exposure of a sensitised subject to the antigen and the resultant reaction.

The delayed allergic states include the sensitiveness developed against various parasitic agents and the dermal contactants like plant resins (e. g. poison ivy), and various simpler chemical compounds. It has not yet been definitely demonstrated that humoral antibodies are related

either to the existence of the delayed state, or to the occurrence of the reaction. The cells which may be involved in delayed hypersensitive reactions seem in general not to be restricted to any particular type. The clinical manifestations of delayed reactions are seen after several hours rather than seconds or minutes as is characteristic of the immediate type.

*Mechanism of Allergic Phenomenon :* The mechanism of allergic response is ill-understood. Various theories have been advanced to explain the allergic phenomenon. It is however, generally accepted that an antigen-antibody reaction is involved.

*The Humoral Theory:* According to this theory, after union of the antigen with the antibody, a cleavage of the resulting combination is produced by the action of the complement, and that this cleavage product which has been termed anaphylatoxin (or serotoxin) has toxic properties and is responsible for the occurrence of anaphylaxis. This theory, however, is unable to provide a satisfactory answer to the various problems involved in this reaction and has been refuted by many authors.

*The Cellular Theory:* As a result of the antigen combination with the fixed antibody in the cell it has been thought that one or more chemical substances (like histamine, acetyl choline, heparin, lysothin, slow reacting substance, and other metabolites) are released which may be responsible for allergic manifestations. Such substances have commonly been referred to as 'H' substances.

When Dale and Laidlaw observed that the action of histamine simulated the reactions observed in anaphylactic shock, histamine was thought to be responsible for the ultimate response. There are many arguments for and against the histamine theory, and though histamine does not account for the whole picture in experimental anaphylaxis, there is yet no other agent to which we can attribute the important phases of the reaction that bring about the fatal issue.

In the delayed forms of allergy, however, as in the tuberculin type or exudative dermatoses such as eczema, other mechanisms besides H substance or histamine are likely to be responsible about which our knowledge is very limited.

Though the part played by histamine in allergic reactions is still a controversial topic, recent discovery of histamine liberators has given a new impetus to further research in this field. It has been observed that syndromes produced by histamine liberators are strikingly similar to those found in allergic conditions. Various antihistaminics are also found to inhibit the manifestations produced by histamine liberators, with the possible exception of gastric hypersecretion. Some of these compounds are active in a wide range of animal species, like compound 48/80 studied by Paton. Others like dextran, ovomucoid, globin are active only in rats, while poly-vinyl pyrrolidone produces symptoms only in dogs. These histamine liberators are supposed to act through a release of endogenous histamine which in turn is responsible for the symptoms observed. These compounds are also able to release histamine from tissues *in vitro*.

Adrenalectomy renders the animal more sensitive to histamine liberators. The adrenal hormones, particularly cortisone, are reported to restore the sensitivity of the adrenalectomised animals to the normal level.

*Protease Activation Theory :* According to Burdon the proteolytic enzyme system of the body plays an important role in the pathogenesis of allergy.

In the body fluids and the tissues proteolytic enzymes are present and these and their precursors exist in balance with the antiproteolytic factors. The antigen-antibody reaction which may occur in the blood or locally in the tissues acts as a trigger mechanism for the activation of these enzymes. These in turn cause cellular damage, releasing histamine, acetyl choline and other products which are responsible for the manifestations of anaphylactic shock and possibly other allergic manifestations.

There is no definite evidence to show that the proteolytic-antiproteolytic system plays a part in the localised phenomenon of allergy. However, since similar systems do exist in the tissue as well as in the blood, the extension of the theory to include them appears tempting.

Copenhagen and MacDowell find sodium-potassium imbalance as the essential feature of the phenomenon of hypersensitivity. They suggest that in allergic states the body is deficient in sodium as a result of adrenal insufficiency and the smooth muscles become abnormally excitable, hence they react very violently to histamine. The adrenal hormones which mobilise potassium and retain sodium, restore, through this electrolyte shift, the normal excitability of the cells.



## Allergy

The basic mechanism involved in allergy appears to be the production of antibodies. The capacity to produce antibodies is an important protective mechanism against infectious agents. The life-long immunity which follows an attack, and subsequent recovery from infectious diseases like measles and yellow fever, show the favourable aspect of the genesis of the antibodies.

However, the antibodies do not always have such beneficial, protective effects. In an allergic individual interaction of the antigen with the antibody can cause cellular damage, resulting in structural and functional disturbances, characteristic of the allergic state, which is quite different from the primary noxious effects of that agent.

Certain individuals susceptible to allergic diseases produce antibodies even to a great variety of inanimate and otherwise harmless allergens. The production of antibodies against allergens of this kind serves no useful purpose. On the contrary, subsequent contact with the noxious agent causes cellular damage which manifests as localised or generalised allergic disease. The initial contact with the offending allergen may not be always obvious.

If then, allergy is due to the presence of antibodies, the problem of allergic sensitization is largely that of antibody production.

The important question concerning the site of antibody formation is still unsolved. Macrophages, other reticulo-endothelial cells, lymphoid cells, lymphocytes or plasma cells all have been incriminated. The fact that any one type of cell is concerned is without proof. It is becoming increasingly realised that the various types of cells and the various tissues and organs take part in the antibody formation. The important investigation with labelled antigens and with fluorescein-labelled antibodies as an indicator for the localisation of antigen in the tissues, has revealed the presence of the injected antigen in the phagocytic cells such as Kupffer cells, in the reticulum cells of the lymphoid and the splenic tissue, and in developing lymphocytes but not in polymorphonuclear cells. Further investigations with these methods will probably throw more light on these problems. F. Haurowitz (1953) assumes that since all cells produce proteins, all of them are also able to form antibodies provided they can trap the antigen and store it without destroying it.

From the point of view of biochemical mechanisms involved in the production of antibodies, three different theories have been advanced.

*Antigen Template Theory* : According to this, the antigen itself becomes an integral part of the globulin synthesizing unit (GSU). The antigen is deposited at the site where serum globulins are formed, amino-acids are fitted into appropriate pattern on the antigen and synthesized into a protein which is the antibody.

*Adaptive Enzyme Theory* : The antigen induces a change in the existing GSU and at the same time induces it to produce antibody and replicate.

*Natural Selection Theory* : The antigen selects from a wide variety of existing GSU those with which it has greater affinity and induces them to produce antibody and replicate.

The antigen template theory is probably the most widely held at this time. The recent concept of antibodies as a diverse group of naturally occurring proteins indicates that the antigens selectively stimulate the production of those natural proteins for which it happens to have the greatest affinity.

As regards the nature of allergic humoral antibodies the recent data are in agreement with the view that they are found principally in the  $\beta$ -globulin fraction.

According to Winer, univalent antibodies are involved in the immunity against the pathogenic germs, while the bivalent antibodies play the essential role in allergic phenomenon. In hypo-sensitization treatment, not only does the titre of the antibodies tend to rise, but the quality changes and the amount of univalent (blocking) antibodies become prevalent. The allergic manifestations follow the interaction between the antigen and the bivalent antibodies, while its association with the blocking antibodies is symptomless.

The effect of the adrenal hormones on the rate of antibody production has been studied. In general, the conclusion is that antibody production is depressed by ACTH and cortisone.

Recently it has been shown that the production of antibodies can be interrupted by antibiotics.

*Histology of Allergic Lesions* : M. G. Bohrod points out that "all of the lesions seen in allergy are also seen in non-allergic conditions and that there is no pathognomonic lesion characteristic of allergy".

According to Bohrod, allergic lesions can be divided into the following groups on the basis of the predominant histologic feature. Thus necrosis may be present in almost all the lesions, but dominates in the necrotising ones.

(1) **Anaphylactoid lesions** : Predominant feature of anaphylactoid lesions is exudation. Allergic coryza, serum sickness, asthma, hay fever and periarteritis nodosa are clinical examples of this group.

(2) **Necrotising lesions** : Here the predominant feature is necrosis. Necrotising lesions have marked clinical and anatomical resemblance to the Arthus and Schwartzman phenomena of experimental immunology, and it is now generally believed that they are expressions of the same mechanism in the human being.

Necrotising lesions may be tissue selective, e.g. cortical necrosis of the kidney, acute pancreatic necrosis or may be cell selective, e.g. thrombocytopenic purpura and granulocytopenia.

(3) **Granulomatous lesions**: These are characterised by nodular inflammatory reaction. The main characteristic feature of the allergic granuloma is the necrotic centre and the radially arranged histiocytes about the necrosis. Allergic granulomas are further distinguished into two types on the basis of the necrosis seen. The tuberculoid type is characterised by caseous necrosis where the necrosis occurs in the inflammatory tissue itself, e.g. in tuberculosis, brucellosis, and beryllium granuloma. In the rheumatoid type, necrosis may occur in the pre-existing tissue, usually collagen, or other connective tissue and the original architecture may be seen, e.g. in rheumatic fever and rheumatoid arthritis.

(4) **Hyalinoid lesions** : These are characterised morphologically by hyaline transformation or deposit in or about the collagen. This group includes collagen diseases and amyloidosis.

There is no cell pathognomonic of allergic lesions. Nevertheless two types of cells need special emphasis. *Eosinophil leucocyte* : It has been considered as one of the important manifestations of allergy, more so of the anaphylactoid type. Bone marrow eosinophilia is more constant and striking compared to peripheral blood eosinophilia. Still more constant is the tissue eosinophilia which may be present even in the absence of the blood or the bone marrow eosinophilia. The presence of eosinophils in the secretions ("secretion eosinophilia") has been utilized as a diagnostic aid. The function of eosinophils in allergy is still not definitely known. It has been thought to carry antigens or to carry histamine or some other cause of the allergic reaction. *Plasma cell* : Recently much emphasis has been laid on the plasma cell as being the 'typical cell' of allergic reactions. Plasmaecytosis is a common accompaniment of human allergic disease.

**Clinical Allergy**:- Human allergy expresses itself in a diversity of ways.

**Respiratory Allergy**: Recently it has been emphasized that the changes in the elastic and viscous properties of the lung tissue, rather than the bronchospasm are responsible for the ventilatory difficulties experienced in bronchial asthma. The changes in the elastic and the viscous properties are due to the oedema and excessive mucus formation, resulting in an incomplete obstruction which is so characteristic of bronchial asthma.

Antihistaminic drugs have been found ineffective in all except the mildest cases of bronchial asthma. The formerly considered bronchospasmolytic drugs are now thought to act more as decongestants rather than bronchodilators.

Particular emphasis has been laid on the detection of the offending allergen and specific desensitization against it.

Pulmonary function tests are gaining widespread clinical interest owing to their important bearing on bronchial asthma and emphysema resulting from allergies of the respiratory tract. Most of them are too elaborate, technically complicated and not very useful to the clinician. A few basic tests can serve as diagnostic and prognostic aids and permit one to follow the course of the disease. Recording of the timed vital capacity is regarded to be more significant than the static vital capacity.

Allergy to inhalation of pollens, mould spores and dust is observed frequently. Kasliwal and associates noted a high incidence of allergy in Rajasthan and have found pollens and house dust as common causes of clinical hypersensitivity in this state.

**Cutaneous Allergy** : Allergic aetiology can be demonstrated in a good number of cases of urticaria. The role of acetyl choline in the pathogenesis of physical urticaria has been suggested.

## Allergy

Recent work indicates the possibility of the existence of cellular antibodies in allergic contact dermatitis.

*Haematologic Allergy* : Allergic purpura has been explained through an immunologic mechanism. In sedormid purpura, the drug combines with the platelets conferring upon them the property of the antigens which then stimulate the production of antibodies. These antibodies cause lysis of platelets in the presence of the complement.

*Cardiovascular Allergy* : In cardiovascular allergic manifestations tobacco plays a role of major importance. The source of sensitization is to be found not only in smoking, but also in the tobacco dust which abounds the atmosphere. Peripheral vascular disease (thrombo-angiitis obliterans, migrating thrombophlebitis), and even cardiac arrhythmias have been attributed to tobacco allergy.

*Food Allergy* : In food allergy diagnosis of the aetiological agent is a difficult problem. Only careful history supplemented by diet elimination technique is of diagnostic value.

*Drug Allergy* is a topic of great importance in the present era of new medicines, with formulae of increasing complexity. Stress has been laid on the sensitivity to antibiotics which is usually induced through the topical application of these agents in patients subject to other allergies. Their indiscriminate use in such persons is therefore cautioned.

*Role of Allergy in the Pathogenesis of Certain Diseases* : Recently attention has been drawn to a group of diseases for which hypersensitization has been suggested as a possible pathogenetic mechanism involved.

The various collagen diseases like systemic lupus, polyarteritis nodosa, scleroderma, dermatomyositis, etc. have been suggested to have an allergic pathogenesis. Allergic mechanism has also been thought in thrombocytopenic purpura, due to food or drugs. Likewise, the possibility of allergy as a cause of multiple sclerosis has been suggested.

*Infection and Allergy* : Infection and allergy seem to be mutually related, in as much as, infection increases susceptibility to the allergen, while the allergic condition of the mucus membranes increases the tendency to infection.

Rich believed that bacterial hypersensitivity depends on cellularly bound antibodies. They are not found in great quantities in the circulation and hence passive transfer tests are negative.

Rammelkamp and his associates have found that acute nephritis is almost always caused by haemolytic streptococci type 12 and 4, particularly the former. Recently a similar study by Wilmers et al in Great Britain showed that type 12 was involved in more than 90 per cent of their cases of nephritis.

*Therapeutics* : At present investigation and treatment of the allergic disorder is mainly concerned with the recognition of and precautions against the offending allergen. Once the allergen is recognised then avoidance or hyposensitization against it offers a means of escape. Hyposensitization implies an alteration of the reactive capacity of an individual in such a way that he no longer responds in an abnormal manner even though exposed to the offending allergen.

Though specific hyposensitization is the ideal therapeutic approach yet symptomatic treatment still holds its place. Antihistaminic drugs continue to be used for their palliative relief of the various allergic symptoms. A new antihistaminic, 1-methyl-4-amino-N<sup>1</sup>-phenyl-N<sup>1</sup>-(2<sup>1</sup>-phenyl) piperidine tartrate (available as Sandosten) has been found efficacious especially when used in association with calcium. ACTH and cortisone have been studied carefully and evaluated as to their dosage, contra-indications and untoward effects. They continue to be the basic treatment in status asthmaticus. Results of prolonged treatment with cortisone for more than one year show that this drug can be administered for a long period. Combined treatment with antibiotics is often advisable since recurrent respiratory infections have been noted.

Cortisone though beneficial when administered systemically, is ineffective by local application in allergic eczematous dermatitis. Hydrocortisone, and more recently fludrocortisone, have been found to produce striking effects. For physical urticaria good therapeutic effects with atropine have been described.

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ALLERGY, OCULAR MANIFESTATIONS OF—See OCULAR MANIFESTATIONS OF ALLERGY

AMINOACIDURIA—See RICKETS AND AMINOACIDURIA

AMOEBIC DYSENTERY—See DYSENTERY, AMOEBIC

## AMYOTONIA CONGENITA

E. P. Bharucha

Between 1891 and 1893 Werdnig and Hoffman described the condition which they called 'Infantile Spinal Muscular Atrophy', a familial and lethal form of motor neurone disease starting usually at 6 months of age. In 1900 Oppenheim described a condition of muscular hypotonia and weakness present at birth, non-familial, improving slowly to complete recovery or arrest. He called this 'Myotonia Congenita', later known as 'Amyotonia Congenita'. Brandt (1950)<sup>1</sup> has followed 131 cases diagnosed as amyotonia congenita and recently Walton (1956)<sup>2</sup> has followed 109 cases with this diagnosis. Only 13 of Brandt's cases and 17 of Walton's, in the long term study, subserved the criteria of Oppenheim. The remainder ran a progressive down-hill course indistinguishable from spinal muscular atrophy. More complete paralysis, intercostal involvement, absent tendon reflexes and tongue fasciculations are features which are more in favour of the diagnosis of spinal muscular atrophy. Of Walton's 17 cases, a half recovered completely with no residual hypotonia. The other half showed a certain degree of wasting, lordosis and a waddling gait and Walton considers these identical with cases of 'Congenital Myopathy' described by Aldren Turner (1940-1949). Other conditions producing hypotonia in infancy which must be considered in differential diagnosis are flaccid cerebral palsy, polymyositis, (diagnosed by muscle biopsy), nutritional and skeletal diseases and congenital polyneuritis (characterized by symmetrical, peripheral motor and sensory disturbances and an elevated cerebrospinal fluid protein which persists for several years).

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### ANAEMIA, HYPOPLASTIC, OF CHILDHOOD

R. Subramaniam

In adults pure red cell anaemia may be associated with such conditions as haemolytic anaemia, hypersplenism, thymoma or may arise as a completely idiopathic condition. In the child, one should think of the possibility of chronic infection, renal disease and chronic renal insufficiency, malignancy anywhere, specific haematologic diseases like (a) atypical leukaemia, (b) congenital hypoplastic anaemia, either of the Fanconi type or a so-called pure red cell aplasia. To evaluate the therapy precisely, the extent of erythroid oppression must be ascertained. A favourable response is obtained some times with therapeutic agents like ACTH and other steroids—in cases with moderate normoblasts in the bone marrow rather than in those whose bone marrow was depleted of normoblasts. Similarly, the response occurred in persons in whom the severe anaemia was not present from birth but appeared later in childhood, adolescence or adult life. In these cases splenectomy may be effective. In cases in which bone marrow toxins such as infections, drugs, or chemicals could aetiologically be established, recovery might be looked for following their elimination. Besides ACTH or steroids or transfusion, splenectomy is indicated.

**ACTH and Steroids :** Cortisone, hydrocortisone or prednisone are useful. They are prescribed in the daily dosage of 100, 80, and 40 mg respectively in divided doses. When response occurs it is evident in three or four weeks; the dosage level is arbitrary. When the patient responds the dose is reduced to the minimum which maintains a remission to avoid side effects. With erythroid hyperplasia, reticulocytosis, increased haemoglobin and red cell levels, smaller amounts of the steroids should be tried. Any evidence of infection should be checked by suitable antibiotics. Despite the low haemoglobin level these patients are not unduly susceptible to infection. If no response is obtained with steroids, ACTH may be tried by intramuscular or subcutaneous route. Here also the response varies. Once there is response the dosage should be reduced.

**Transfusion :** A great drawback with regard to transfusion is iron overload of tissues, i.e. haemosiderosis. Transfusion is not required until the haemoglobin level decreases to 7 to 7.5 g/100 ml. Repeated transfusion has a depressing effect upon the endogenous erythropoiesis and haemoglobin synthesis.

**Splenectomy :** It has proved to be of value in some cases, when transfusions are given at frequent intervals to maintain the haemoglobin level. It is presumed that the extra-corpuscular haemolytic component is situated at the spleen level and on this basis splenectomy is advised. Splenectomy results in prolonging the interval between transfusions. Where there is no haemolytic component demonstrated even then splenectomy is indicated on the assumption that the abnormal functioning spleen may depress the erythropoietic function of the bone marrow. This is particularly considered when response to ACTH or cortisone or steroids is poor. These patients are not made worse by splenectomy. Other agents that may be tried are cobalt and factors of the vitamin B complex. Parenteral iron should not be tried as there is already excessive iron deposition in the tissues as a result of repeated blood transfusions. Cobalt has side effects such as anorexia, nausea and thyroid enlargement in children.

The following dosage is suggested for vitamin B factors: 1000 µg for B<sub>12</sub> i.m., t.d.s., 10 mg t.d.s. for riboflavin, nicotinic acid 25 mg and folic acid 5 mg t.d.s. Though their value in this type of anaemia is debated they are occasionally found to be of value in cases in which splenectomy has been done.

Cobalt chloride has been administered in dose of one mg per lb of body weight in a single day and continued as long as three months. Alternatively, it has been employed as injectable cobalt compound, and when this failed, diathermy to the bone marrow and administration of plasma was thought of, to increase the erythropoietic factors. In spite of this, the therapeutic response has been poor.

It was felt that as much information as possible was advisable in the consideration of any anaemic state particularly when there was lack of nucleated red cells.

The main problem is how to make the red cell corpuscles grow. This will depend upon further knowledge of the enzymes, amino acids and humoral factors concerned in erythropoiesis. At the present it has been felt that the therapy is in a very unsatisfactory state.

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**ANAESTHESIA***Janak Mehta and A. J. Dhruva*

Advances in the techniques of anaesthesia as well as the introduction of some new drugs in recent years have made certain surgical procedures possible which was not the case a few years ago. Such new measures have facilitated or simplified other procedures, thus reducing mortality and morbidity in surgical operations.

**Artificial Hypothermia.**—In 1772, Robert Boyle first suggested that cold might be beneficial to the patient in certain conditions. Temple Fay first proposed the use of total body-cooling for malignant disease in 1936. However, the initial work in the research and clinical application of hypothermia was carried out by Bailey, Swan and Bigelow in 1950.

Hypothermia as an aid to anaesthesia is based on the fact that cold reduces the metabolic activities of the organism. There is about five per cent fall in oxygen consumption for each degree centigrade fall in the body temperature. It thus causes marked reduction in the oxygen requirement of the body and a hypoxic patient can be adequately oxygenated under hypothermia. It diminishes the sensation of pain. It considerably reduces the alkaline metabolism, thus minimising the risk of anoxia especially of the central nervous system and reducing drastically the body's reactivity. In addition to oxygen-sparing effect it also depresses enzyme activity.

Autolytic enzyme activation is known to occur readily in the presence of anoxia at normal temperature; at lowered tissue temperature, onset of anoxia is delayed during the failure of oxygen supply and the secondary changes that follow resulting in permanent intracellular disorganisation and death are retarded. Thus, under hypothermia tissues will retain their vitality for a longer time in the event of anoxia as compared to normal temperature. At normal body temperature, the brain can withstand anoxia for about four minutes without appreciable damage, while at 25°C occlusion of great vessels can be safely maintained for about eight minutes. Besides reducing the oxygen requirement and cardiac activity, it increases the coagulation time by causing a fall in the number of platelets and in the prothrombin level. This prevents post-operative thrombosis though it may lead to post-operative haemorrhage. Under hypothermia there is suspension of harmful bacterial and enzyme activity.

There is a fall in the heart rate which may be 30 per minute, reduction in cardiac output and blood pressure and general constriction of the vascular tree. Continuous electrocardiogram is essential to note serious cardiac irregularities which are not infrequent. Respiration is depressed and may stop completely. Depression of the central nervous system may lead to analgesia and coma.

Thus hypothermia may obscure the signs of shock, which is not rare with this technique. Hence, to obviate shock other anti-shock measures like blood transfusion, perfect anaesthesia and use of ganglion-blocking agents have been employed.

It is difficult to diagnose shock under hypothermia as blood pressure does not serve as a guide to the patient's condition. Pulse rate is a good criterion. Local blocks of the pleura and pericardium in thoracic operations reduces its incidence. Also all blood loss must be replaced promptly.

Another serious complication, especially with temperatures below 28°C, is ventricular fibrillation. A cold heart fibrillates much more easily when subjected to epinephrine, asphyxia or trauma, than a warm heart. Some of the causes are deep anaesthesia, respiratory acidosis, poor coronary flow and mechanical irritation of the heart. Artificial hyperventilation to produce respiratory alkalosis is advocated throughout hypothermia, as it has been observed that if respiratory acidosis is returned to normal rapidly, ventricular fibrillation may be precipitated. Hyperventilation reduces serum potassium level. Potassium chloride in the coronary arteries and procaine amide have been suggested as preventive measures. Anticholinesterase neostigmine given by coronary perfusion protects the cold heart against ventricular fibrillation. In the cold state, the parasympathetic is suppressed earlier than the sympathetic. Hence either enhancement of the vagal action or suppression of the sympathetic tends to diminish the incidence of ventricular fibrillation. McMillan states that below 25°C there is a rise in plasma calcium level and this produces electrocardiographic changes which are a precursor of ventricular fibrillation. On the other hand Swan has used calcium chloride successfully to treat cardiac arrest in a hypothermic patient. In the event of ventricular fibrillation cardiac massage should be tried. When the heart muscle is well-oxygenated and its tone is good, electric shocks of 1.5-2 amperes should be applied. Brewin advises injection of 1 c.cm of 1:3,000 adrenaline into

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the ventricular cavity followed by massage. When the tone has improved, a shock of one ampere is applied for one-fifth of a second. Swan uses potassium chloride followed by calcium chloride to restart the action of the heart. Electric defibrillator is thought to be not so effective at low temperatures as at the normal body temperature.

In the early days cooling was done by immersing the patient in cold water bath or putting ice around him. Nowadays, thermotrite circulating water blankets are used for the purpose. The patient is anaesthetised and put on the blanket in which water at 0° C is circulated. Rectal temperature is recorded. However, it is found that the oesophageal temperature approximates the temperature of the heart closely and at some clinics this temperature is recorded. Likewise temperature at the base of the nasopharynx approximates that at the base of the brain. Circulation of cold water is stopped 2-3° C above the desired level as the temperature falls even after the cessation of circulating cold water. Minimum anaesthesia with nitrous oxide and oxygen is administered. Curare is given to minimise the incidence of shivering which increases oxygen consumption 7-8 times. Chlorpromazine has been advocated by some for the same purpose. As soon as the operative procedure to be performed under hypothermia is over, warming of the body is started by running water at 44° C to 46° C till the body temperature rises to 34° C. Diathermy may be used to elevate the temperature.

The technique is used for open cardiotomy—septal defects, aortic stenosis—where the great vessels can safely be clamped without the danger of tissue anoxia for 7½ minutes at 28° C. It is employed for total cessation of circulation to achieve a dry field within the heart. Brock accepts a limit of ten minutes arrest at 28° C. Bailey achieved complete circulatory arrest in an infant for 22 minutes at 21.6° C successfully. It is used in operations where regional ischaemia is desired, e.g., neurosurgery. Here the carotids can be clamped for about eight minutes. In thoracic aneurysm the thoracic aorta can be clamped for about an hour without any damage to the spinal cord.

In extensive burns it has been found to reduce primary shock, decrease oedema, reduce potassium loss and slow protein breakdown.

Of late extracorporeal blood stream cooling has been employed by some. Blood from an artery is circulated through a plastic tube immersed in a cooling mixture and returned into a vein. This is more rapid and can be employed when the operation is in progress and hypothermia found desirable. Rewarming of the circulating blood is easy and leads to early elevation of the cardiac temperature.

Brock and Ross recommend introduction of a catheter through the right atrium into the superior and inferior venae cavae, and blood is pumped through the cooling coil before being returned to the inferior vena cava. For the purposes of rewarming fresh cannulae are inserted and blood is pumped through the coil which is immersed in water at 40° C. Anticoagulants are not necessary as the blood does not coagulate at such a low temperature.

Since the introduction in some institutions, of the heart-lung machine successfully permitting the cardiac bypass, the use of hypothermia has become limited.

**Chlorpromazine.**—This was synthesised by Charpentier in 1950. It is a phenothiazine derivative related to the antihistaminic phenergan and diparcol and was developed while attempting to find out a phenothiazine derivative with greater central depressant action than promethazine. The drug has been very popular for preanaesthetic medication as well as post-operative sedation and comfort of the patient. It has varied actions e.g. relieves vomiting caused by morphia and pregnancy, reverses the pressor effect of small doses of adrenaline and noradrenaline, has a peripheral ganglion-blocking action, has a central depressant action on the reticular formation of the brain which controls vomiting, heat regulation, wakefulness, vasomotor tone, voluntary muscle tone, secretion of the anterior pituitary, etc. It causes sedation without hypnosis and potentiates the action of cerebral depressants. The patient is easily accessible and responds immediately though he lacks spontaneous interest in his environments. There is minimum cortical or higher central depression though agitated patients under their effect go to sleep. In psychiatry reserpine with chlorpromazine has been a favourite combination used for bringing about chemical leucotomy.

Chlorpromazine prevents shock by causing autonomic block and causes lowering of temperature by reducing heat production due to sedation and causing increased heat loss by vasodilatation. It is used in paediatrics for operations like tonsillectomy, cardiac catheterisation, endoscopy, etc.

Usual dose is one mg per kg body weight. "Lytic cocktail," i.e. chlorpromazine 50 mg, promethazine 50 mg and pethidine 100 mg, is a common form of premedication. Some replace chlorpromazine with hydergine and claim that this causes less clouding of consciousness and has fewer local irritant effects.

Toxic reactions to chlorpromazine are reported. Some of these are nausea, anorexia, epigastric pain, jaundice, agranulocytosis and severe fall of blood pressure. Tolerance may develop necessitating increased dosage.

Cohen and Beecher disagree with the common view that premedication with narcotics lowers the metabolic rate so that anaesthesia becomes easier. They believe that unless pain is present no narcotic should be given and adequate premedication is achieved with atropine and barbiturates.

**Controlled Hypotension.**—Several methods are employed to secure a bloodless field of operation e.g. tourniquet, infiltration of a vasoconstrictor, high or total spinal analgesia, arteriotomy. One such method is the employment of ganglioplegic drugs.

The aim of induced hypotension, besides reducing the blood loss and creating a bloodless operative field, is to obtain a neuro-vegetative anaesthesia which protects the individual against anoxia and shock which may develop due to disorderly peripheral vasoconstriction.

Drugs used for the purpose are procaine, methonium salts, arfonad, phenothiazine derivatives and piperidine derivatives. Hexamethonium bromide leads to tachycardia and the fall of blood pressure is not marked. Pentolinium causes profound hypotension and is longer-acting but the pressure falls slowly. If the initial dose is too large there is severe fall of blood pressure; if too small, there is no desired level of hypotension. The average dose of hexamethonium is 50-100 mg, of pentolinium tartarate 10-20 mg and arfonad, 30-50 mg. These have to be less if the patient is hypertensive to avoid dangerous fall in the blood pressure. Initial response to the drug has to be assessed in each case.

Arfonad is used very frequently as one can definitely control the level of blood pressure by giving it in regulated intravenous drip in five per cent glucose, one mg per c.cm. It is a thiophanium derivative, and has a direct effect on the vascular wall, as well as, sympathetic ganglia, impeding the transmission of impulses by increasing the threshold of receptor cells for acetyl choline. On stopping the infusion blood pressure returns to normal. But some patients are resistant to the drug and others develop marked hypotension which is not readily reversible. Local and systemic effects due to histamine release, like perivenous redness and swelling along the course of the vein, headache and malaise may also be observed. There may be an increase in free acid level in the gastric juice.

The lowest permissible pressure at the heart level should not be less than 60 mm of Hg. This maintains adequate cellular respiration and metabolism provided there is vasodilatation and full oxygenation. The myocardium does not tolerate hypotension below 40-60 mm Hg. especially if it is associated with suboxygenation. With a head-up position there are chances of cerebral ischaemia. Elevating the site of operation above the level of the heart lowers the blood pressure in the field of operation while maintaining safe pressure at the heart. For effective maintenance of hypotension, carbon dioxide must be eliminated thoroughly. Apapnoea induced by hyper-ventilation assists in maintaining the low blood pressure. Controlled respiration leads to the fall in blood pressure by decreasing cardiac output and venous return to the heart. Therefore, some prefer to keep the patient breathing on his own. The greater the fall in blood pressure, the higher is the incidence of complications. Majority of them are due to the derangement of the functions of the brain, liver, heart and kidneys. The technique should preferably be avoided in patients with marked arteriosclerosis and in those where there is a history of coronary, cerebral or renal insufficiency, as complications like anuria, cerebral and coronary thrombosis are reported. Visual disturbances, vertigo, nausea, headache and intestinal atony may follow. Suboxygenation with hypotension is very dangerous and may lead to cardiac arrest. Barbiturates, muscle relaxants and posture cause a fall of blood pressure and a ganglion-blocking agent may not be necessary. Signs of excessive hypotension like uneven, gasping or Cheyne-Stoke's respiration, irregular pulse and bone-dry operation field should be guarded against. Duration of hypotension should be the minimum required. The common drugs employed to achieve hypotension are parasympathomimetic and the incidence of bronchospasm leading to death has been reported. A hypotensive patient does not tolerate even slight overdosage of sodium pentothal or short periods of mild anoxia which may be of no consequence in a normal patient.



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The technique is used with advantage in operations like cleft-lip, dacryocystorhinostomy, operations on the head and neck, e.g. block dissection of the glands of the neck, rhinoplasty, plastic operations on the hand and radical mastectomy. Either alone or along with hypothermia it is used in neurosurgery and for the surgery of vascular tumours.

**Viadril.**—When a steroid hormone was injected into the peritoneal cavity of rat by Hans Selye in 1941 it was observed that the animal promptly went to sleep, became limp and did not react to potent stimuli. In about forty-five minutes it was fully awake and running about in the cage, apparently none the worse for this period of anaesthesia.

The production of anaesthesia by the injection of a steroid compound, 21-hydroxy pregnandione sodium succinate (Viadril) is rather fascinating. The use of the drugs which are similar chemically to the compounds elaborated physiologically in the body is perhaps a step towards solving the enigma of the narcotic state.

Viadril has been tried in recent years to produce anaesthesia with or without supplementation with the known anaesthetic agents. A predetermined dose is given intravenously as 0.5 to 1 per cent solution in normal saline or five per cent glucose solution in normal saline. Anaesthesia is achieved in five to fifteen minutes with slight to moderate depression of respiration but with increased respiratory rate in most cases. Induction is quite pleasant without the patient's knowledge as to when he went to sleep and he wakes up early with relatively mild or at times none, post-anaesthetic sequelae like nausea, vomiting and depression. The drug has no hormonal effect. Like pentothal sodium it is a nonanalgesic hypnotic and anaesthesia produced is by virtue of its narcotic effect. Its mechanism of action is not fully understood. The difference between Viadril and sodium pentothal is the marked depression of the pharyngeal and laryngeal reflexes accompanied by a variable degree of muscle relaxation which appears with the steroid compound. This obviates the possibility of laryngospasm and intubation is easy with the patient breathing regularly and spontaneously. However, Viadril is not without drawbacks. It produces thrombophlebitis and thrombosis at the site of injection. It has a longer time of onset viz. five to fifteen minutes after intravenous injection. The effect of a given dose is unpredictable and may lead to a marked alteration in the respiratory and cardiovascular systems, e.g. fall of blood pressure, rise in pulse and respiratory rates and, at times, apnoea. Its effects are not easily reversible. There is a long interval between the injection of the drug and the appearance of undesirable side effects. Hence fractional method is not always successful. It resembles pentobarbitone more than thiopentone or pethidine.

Further clinical trials will prove the usefulness and limitations of the drug.

**Xylocaine.**—This drug is slowly replacing procaine as a local and regional anaesthetic. It has an intense analgesic action combined with great blandness to the tissues and exceptional stability through a wide range of pH. It has a far shorter period of onset, longer duration of action and greater spread through the tissues than procaine. Thus addition of hyaluronidase is not necessary. As a surface analgesic it is remarkably safe, efficient and free from allergic reactions. It is neither a vasoconstrictor like cocaine nor a vasodilator like procaine. Its toxicity varies with its concentration. It is equal to procaine in 0.5 per cent solution but is twice as toxic in a 2 per cent solution. Being much more potent than procaine its concentration required is much less. It is frequently used for spinal and epidural analgesia.

**Muscle Relaxants.**—The mode of action of various muscle relaxants is now well-established. Tubocurarine acts by combining with the protein molecules of the motor endplate and preventing excess of acetyl choline to this region and depolarisation of the endplate. This is termed 'competitive inhibition' or 'non-depolarisation block'.

The action of this group of drugs is reversed by anticholinesterase drugs. Decamethonium and succinyl choline bring about depolarisation themselves and cause fasciculations. After a brief period of depolarisation of the endplate, this region remains in a state of altered sensitivity so that it requires an endplate potential several times greater than normal before further depolarisation can take place. This is known as 'depolarisation block'. The block is increased by anticholinesterase drugs.

A mixed block occurs when both depolarising and non-depolarising agents are used in the same patient. It is a common practice to give succinyl choline for intubation and then follow it up with tubocurarine for further relaxation. Here some endplates are under the effect of depolarising drug while others are affected by a non-depolarising drug. This might lead to prolonged paralysis.

Thirdly, at times a dual block may occur where a motor endplate responds first by depolarisation and then by non-depolarisation. It has been shown that these depolarisation and non-depolarisation blocks are antagonistic. If 5-7 mg of d-tubocurarine is given, the dose of succinyl choline required to abolish respiration is much more than normal. When succinyl choline is given in repeated doses, e.g. by intravenous drip, the paralysis can be reversed by neostigmine.

A case is reported by Bulloch where after induction of anaesthesia with thiopentone, scoline 50 mg was given for intubation. There was complete respiratory paralysis even after 30 minutes. Ten mg tensilon was given which led to spontaneous breathing. But it was only temporary and lasted for 20 minutes. Respiration was inadequate for 5½ hours. Two and a half mg prostigmine was given which improved the breathing. After 7½ hours, breathing became shallow and responded to tensilon. Thus a dual block may occur after a single injection of succinyl choline which can be reversed by tensilon. It is again observed that after a second injection of succinyl choline there are no fasciculations. Due to fasciculations caused by succinyl choline there is generalised body pain. Some advise slow injection to reduce its incidence and rest in bed for 24 hours.

Prolonged apnoea after a muscle relaxant may be due to central depression by drugs like pethidine or due to respiratory alkalosis due to hyperventilation. Also, if there is some acidosis due to CO<sub>2</sub> retention there will be depression of the respiratory centre. Prolonged apnoea with succinyl choline may be seen in diseases of the liver where there is low serum cholinesterase.

Cases are reported where the effect of d-tubocurarine is not neutralised by the anticholinesterase drug. Hunter calls this 'neostigmine resistant curarisation'. This may be due to low intracellular potassium.

With a view to finding a short acting muscle relaxant with a non-depolarising agent having an antidote, drugs like prestonal are under trial. It seems to be acting by a dual block. It is claimed that pyridostigmine shows some antagonism to it.

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#### ANTIBIOTICS

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Antibiotics have revolutionised the therapy of infections. They have also revolutionised the behaviour patterns of microbes. It is the inherent resistance of certain organisms to known anti-

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biotics and the altered response of those which were sensitive, that goad us on for further investigations and trials in a search for more and effective members of the group.

This short review is divided mainly into the following three sections: (1) Newer knowledge about older antibiotics, (2) Newer antibiotics and (3) Combination of antibiotics.

*Chemical Synthesis of Penicillin:* For the last one decade effort was being made to synthesise penicillin and only recently was it crowned with success. J. B. Sheehan and his associates have accomplished at the Massachusetts Institute of Technology the first ever synthetic penicillin. It was the unstable nature of the penicillin molecule that proved to be the greatest obstacle in its synthesis. At present ten new kinds of synthetic penicillin are being tested for possible future use. Even though no one envisages the fact that this synthetic penicillin may be cheaper than the natural penicillin, yet it is hoped that these new forms will prove effective against micro-organisms now resistant to natural penicillin and against a wider variety of infections. It is also hoped that it may produce less of allergic reactions.

*Mode of Action of Penicillin:* Park and Strominger (1957) working with radioactive penicillin have discovered that the antibiotic acts by interfering with the formation of the bacterial cell membrane. Earlier studies have shown that the bacteria failed to complete their reproductive cycle, if they were bound with penicillin. The bacterial cell was prevented from developing the protective membrane, which is necessary for the fragile body. This mode of action of penicillin has opened up an enormous potential scope for the development of future chemicals against the bacteria, since it is now known that there are two or three biochemical structures in the cell wall that are unique to bacteria and non-existent in animal tissues. This fact will make it possible to develop chemical analogues to these substances, that will be nontoxic to animals and man.

*Oral Penicillin :* To have a preparation of penicillin effective on oral administration, was the wish of both the doctor and the patient and this was particularly felt when penicillin had to be used on a prophylactic basis against rheumatic fever. The buffered tablet of potassium penicillin G which was in use for the last two to three years, has been to a very great extent superseded by phenoxymethyl penicillin (penicillin V). It is significant to point out that penicillin V was being widely used in Austria and Germany since 1952. Phenoxymethyl penicillin is relatively stable and insoluble in acid, but is converted to a water-soluble salt in an alkaline media. This facilitates absorption at the intestinal level with no destruction at the gastric level. It is assessed that one milligram of phenoxymethyl penicillin had an activity approximately equivalent to that of 1700 units of benzyl penicillin. It has also been found that phenoxymethyl penicillin was absorbed slowly, the peak concentration being reached only after one to two hours, and an average effective concentration was maintained for a longer time than benzyl penicillin. The blood level tended to be higher if it was given after food. The total daily dose of phenoxymethyl penicillin by mouth should be at least twice the dose of crystalline penicillin administered parenterally. The allergic and other side reactions have been found to be much less common than in parenteral penicillin which will really be a definite advantage for the oral administration.

*Synnematin B (Cephalosporin N) :* This is a new penicillin produced by a species of cephalosporium, which has an activity against certain species of Gram-negative organisms, especially salmonella. This is an action which is probably unique to this penicillin. It is effective against Gram-positive cocci also. A few cases of typhoid and paratyphoid A in man have been successfully treated with this. Like penicillin G pure penicillinase as well as penicillinase producing staphylococci and Gram-negative bacilli nullify its antimicrobial action. Nevertheless Synnematin B is of particular interest because it has action against Gram-negative organisms and because it can control salmonella infection in experimental animals more effectively than does chloramphenicol.

*Penicillin Reactions :* In the last few years reactions due to penicillin therapy have become more and more common. They have assumed an important and serious position because of the increased mortality as a direct result of penicillin administration, apart from other serious and alarming symptoms. It has been found that penicillinase which destroys penicillin can very much minimise the sensitivity reactions. Antihistamines have proved to be of limited success and the incidence of delayed reactions did not seem to be influenced by them. Factors that favour penicillin sensitivity include previous administration of the antibiotic and a personal

or family history of allergy. It is not easy to predict the duration of sensitivity. Milder types of sensitivity are likely to clear up spontaneously in a few months or a year or two. Depot penicillin induces sensitization oftener and more seriously than other preparations. Administration of cortisone has proved to be helpful in preventing or treating the reactions.

**Complications of Streptomycin Therapy.**—An important and interesting observation has been made about the toxic effect on the eighth nerve during the administration of streptomycin. In a study of 102 patients with an average period of treatment for 38 months Witchell has observed that only 8 patients had complained of defective hearing. It was noted that the hearing loss was detected much more frequently among the older patients. The incidence was 21 per cent in the age group 13-29 years and 62 per cent in 50-59 years.

Another interesting complication observed during the continued administration of streptomycin in children was the finding of local lipodystrophy as seen after insulin injections. In the particular series noted by Midulla, there were 7 cases.

**New Salts of Tetracycline.**—The phosphate and metaphosphate salts recently introduced (Kaplan, 1957) have the advantages of surpassing the hydrochloride salt of tetracycline in speed and efficiency of absorption with resultant higher and larger sustained blood serum and body fluid levels. It has been found that dosage of 500 mg twice a day was adequate in most infections which made the frequency of administration much less.

Antibiotics have so far made little headway against virus infections except against psittacosis, trachoma, and lymphogranuloma, and no new antibiotics have come into the field. Psittacosis can be successfully treated and eliminated with Aureomycin or Achromycin.

**Newer Antibiotics.**—*Novobiocin*: The tendency of many organisms especially *Staphylococcus aureus* to show resistance to established antibiotics, has made the introduction of newer products a matter of considerable importance. Novobiocin produced by *Streptomyces niveus* and identified structurally as the glutamate salt of a sugar derivative is available for clinical use as the monosodium salt. It has potent action against staphylococci, whether sensitive or resistant to other antibiotics. It does not show cross-resistance with any other agents. A study of its activity *in vitro* indicated that it was active against most gram-positive cocci. This should be particularly useful against penicillin-resistant staphylococci. Resistance of staphylococci to novobiocin can be induced *in vitro* and has been observed in treated patients. Such strains have already been isolated in the U.S.A. Given orally, the absorption of this antibiotic varies greatly in different people, the exact factors governing this varied response being unknown. Once absorbed there is a notable binding of novobiocin to serum proteins, but this does not reduce the antibacterial activity. The adequate average daily dose of this has been found to be 0.5 gram twice a day. This dose is effective in most of the infections. The important disadvantage noted with its administration is a mild toxic symptom manifested by a skin rash, which may appear with or without fever. In a study of 348 cases the skin rash was observed in 31 cases (8.9 per cent). This rash is likely to occur only when the daily dose is 2 grams per day or more and when the drug is administered for more than 6 days. To circumvent this novobiocin is now combined with an equal part of penicillin, which in effect essentially means a lower dose of the drug per day.

*Vancomycin*: This is a new antibiotic introduced in 1956 by Geraci et al. It is obtained from *Streptomyces orientalis*. It is an amphoteric substance with a rather complex structure that forms a water-soluble crystalline substance with hydrochloric acid. Its range of activity is one which closely resembles and is very much similar to that of penicillin. This activity is not significantly altered by a change in the pH, or by the presence of serum. No cross-resistance has been observed between this antibiotic and the older well-established ones. The main indication of this new antibiotic is against *Staphylococcus aureus* which has already become resistant to other antibiotics. It is administered by the intravenous route, although it may be given by the intramuscular. Oral administration is useless because its absorption from the gastro-intestinal tract is very erratic and the drug is not absorbed. Gram-negative flora of the intestinal tract is not affected, while *Streptococcus fecalis* is very much reduced in number. Emergence of yeast infections and mucocutaneous moniliasis have not yet been observed.

The various complications observed during its therapy are drug fever, renal irritation and dermatitis. Another important complication, which to a very great extent depends on the

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mode of administration, is localised irritation and thrombophlebitis. Intramuscular administration may obviate this important complication. It has been found effective in the treatment of severe cases of staphylococcal infections, including micrococcal diarrhoea and enterocolitis. For the latter infection it would seem to be the drug of choice, because of its bactericidal effect and because large quantities are excreted in the stools on account of its very poor absorption in the intestinal tract. The most important field in which both novobiocin and vancomycin will be very beneficial is against resistant groups of staphylococci, and the virtual restriction of these for such treatment has been suggested.

*Streptovaricin* : This is a new streptomyces-produced antibiotic, which is isolated from a fungus found in a soil sample from Dallas, Texas. Its potential scope lies in its effectiveness in the treatment of tuberculosis. Reported for the first time in February 1957 in St. Louis, this antibiotic promises to be a very effective remedy against tuberculosis. In animal experiments it was found to be more potent than streptomycin or p-aminosalicylic acid, but less effective than INH. Apart from its direct effect on the tubercle bacilli, it has a very important role in potentiating the effects of INH. The experimental success on this score has been stated 'remarkable'. But it is to be noted that the effect of streptovaricin therapy alone in tuberculosis is by no means remarkable.

*Nystatin* : This is an antibiotic isolated from *Streptomyces noursei*, and was found to have antifungal properties. Not only that this has antifungal properties but it is the first antibiotic to show unquestionable and constant effects on experimental histoplasmosis, without producing toxic effects. It was tried in the treatment of moniliasis in 122 cases. In only 5 of this series was it a failure. Topical application has given very good results.

*Albomycin* : This iron-containing peptide was first isolated in 1951, from cultures of the streptomycete, *Actinomyces subterraneus*. This has been found to be particularly effective against staphylococci which are resistant to other antibiotics. It has been found to be ten times more potent than penicillin. Albomycin has proved to be very effective in the treatment of pneumonia and pneumococcal meningitis, particularly in children.

*Fumagillin* : This is an antibiotic elaborated about three years ago. This is produced by certain strains of *Aspergillus fumigatus*. It has not gained much of popularity since then. It has been found to have very good action against *Entamoeba histolytica*. Against other bacteria its action has been found to be very minimal. The drawback in the administration of this drug is that it produces severe nausea and loss of appetite. The average effective daily dose has been put down as 30-60 mg divided into four equal parts.

**Combination Therapy.**—The so-called new era in the antibiotic therapy, wherein synergistic and additive actions of two individual antibiotics are made use of in a combination, by which the toxicity is very much reduced, has already been ushered in. But as yet, apart from one or two, the combinations do not seem to work out any miracle, as had been expected or professed.

*Tetracycline-Nystatin* : This new combination wherein the two are combined in the proportion of 250 mg of tetracycline and 250,000 units of nystatin has been done with the idea of preventing the overgrowth of monilia which may occur due to the tetracycline therapy. Nystatin by mouth is effective in the bowel, much less effective in the throat and without much effect in sputum. Kligman and Parker (1956) consider that it is illogical to suppress these fungi on a purely bacteriological basis without a clinical justification, an exception being thrush and vaginal moniliasis. According to Parker a generalised moniliasis is very seldom encountered except in patients with leukaemia, debilitating diseases, in premature infants and in long continued antibiotic therapy. One fact that should be noted is that nystatin is not very effective against established generalised moniliasis.

*Oleandomycin-Tetracycline* : It was in 1954 that oleandomycin was first described as an antibiotic derived from *Streptomyces antibioticus*. This closely resembles erythromycin in its range of activity. More recent studies have shown that this antibiotic exhibits cross-resistance with erythromycin. It has also been found that weight for weight it is far less active against staphylococci than erythromycin. A comparative study of anti-staphylococcal and anti-streptococcal activity of plasma of normal subjects after oral doses of penicillin, oleandomycin and combination of these, showed that penicillin produced highest peak values and the greater total amount of activity than oleandomycin or a combination of it. Oleandomycin has now appeared in the market as a 1 : 2 mixture with tetracycline, under the name of Sigma-

mycin (Synermycin in India). This mixture is claimed to have a 'two-dimensional' spectrum against staphylococci. This means that this combination of antibiotics delays the acquisition of resistance and that the effective action is synergistic for strains of staphylococci. A lot of criticism has come into the field against this combination of antibiotics. Finland and Welch (1957) have shown that this combination does not prevent resistance to one of them, and that no advantage is derived from its use if the organisms are resistant to either member. The important drawback pointed out against this combination is that the use of this preparation in hospitals will result in the exposure to oleandomycin of organisms already resistant to tetracycline, thus enabling the development of oleandomycin-resistance. And because of possible cross-resistance to erythromycin, the use of this combination will knock out the possibility of treating tetracycline-resistant staphylococci with erythromycin wherein comes the specific need of this antibiotic in the present day. So a warning has been sounded that the indiscriminate use of this combination in hospitals carries with it the risk of reducing our antibiotic armamentarium than an apparent extension. In general practice, where staphylococcal resistance produces no problem this combination therapy affords no advantage over the use of effective individual antibiotic.

**Antibiotic-Corticoid Therapy.**—The use of corticotrophin and cortisone in very severe acute infections together with antibiotics has been in vogue for the last few years. Reviewing the results of such a therapy in the hospitals for a period of six years, Lepper and Spies (1957) could not find a lowering of mortality rate. They also noted a high incidence of serious secondary bacteraemia is 15 per cent of the cases. On the whole there is no clear-cut evidence of unqualified good results occurring from this combination. It remains to be worked out as how best we could get the maximum beneficial effects from this combination without the usual side effects.

**Prophylactic Antibiotic Therapy.**—The experience of the effectiveness of the antibiotics in controlling most of the infections has made their extensive use in the prevention of these infections a natural corollary. It has been estimated that in the U.S.A. about 70 per cent of all the antibiotics used are for prophylaxis than for the real treatment of established infections. From the available data it is very difficult to reach any conclusions as to their real worth and effectiveness in the field of prevention, even though in some instances prophylactic antibiotic therapy has been successful. The protagonists in favour of antibiotic prophylaxis even in the absence of definite proof argue that it may do some good and that it does little harm. Arguments against this kind of prophylaxis are: (1) widespread use of antibiotics has contributed to the emergence of strains of bacteria which are resistant to the commonly used antibiotics; (2) the organisms against which protection is desired may be resistant to the antibiotic even to start with; (3) fungal infections or other secondary infections may develop; (4) the patient is exposed to the risk of sensitization and other toxic actions. One of the commonly used antibiotic for prophylaxis is penicillin. It is easy to understand in the light of our recent knowledge of penicillin as to why it should fail. It is widely accepted now that penicillin is essentially a bactericidal in action and that it acts on the growing or multiplying bacteria, with limited action against mature ones. When the idea is prevention there is only very little multiplication or perhaps no multiplication at all of the bacteria, and that essentially means the scope of action of penicillin is nil. Against  $\beta$ -haemolytic streptococci and gonococci penicillin has been most successful. Weinstein (1955) has reported that bacterial complications in measles could not be prevented effectively by antibiotic prophylaxis. Blahey (1952) did not favour tetracycline prophylaxis in catheterised patients undergoing surgery. In majority of other surgical conditions also the prophylaxis with antibiotics has not been found to be successful or helpful. In our present day knowledge indiscriminate use of antibiotic prophylaxis with the fond hope of preventing infections has neither the scientific backing nor reasonable results to support it.

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## ANTIDIABETIC DRUGS, ORAL (ALSO SEE DIABETES MELLITUS, TREATMENT OF, WITH INSULIN)

F. P. Antia and R. H. Dastur

Diabetics pray for an oral drug which would do away with diet and insulin injections. They are thus ever willing victims of quacks who promise them a liberal diet without any injections. The only oral drugs which have been generally acclaimed to be useful are sulphonylurea derivatives.

**History:** Janbon et al<sup>31, 32</sup> were the first to observe the hypoglycaemic effect of a sulphonamide derivative, sulfa-amido-thiodiazol, while treating cases of fever. Later they observed that these drugs produced hypoglycaemia within 3 hours of administration and the effect lasted for 24 hours. Loubatieres<sup>34, 35</sup> found that the drug was inactive in depancreatized dogs so he concluded that the pancreas was necessary for its action. It had no effect on the liver or kidney. Franke and Fuchs<sup>25</sup> and Bertram et al<sup>9</sup> observed the therapeutic response in diabetics.

**Pharmacology:** The two commonly used compounds are (i) N-(4-amino-benzenesulphonyl)-N'-butyl-urea or carbutamide, also known as BZ-55, "Invenol" or "Nadisan". (ii) N-(4-methyl-benzenesulphonyl)-N'-butyl-urea or tolbutamide, also known as D 860, "Rastinon" or "Orinase".

Carbutamide is a powerful bacteriostatic against shigella, salmonella and E. coli<sup>42</sup>. A high bacteriostatic and therapeutic level is quickly reached.<sup>1</sup> Because of its powerful action on E. coli, a high dosage if consumed for a long time may adversely affect the normal intestinal flora.

Tolbutamide resembles carbutamide but it lacks the p-amino group on the benzene ring and because of this structural difference tolbutamide has no antibacterial action.

In a diabetic, insulin is merely a substitution therapy which reduces blood sugar irrespective of the state of the pancreas. The mode of action of sulphonylurea on the other hand is through stimulation of the functioning pancreas. Insulin therapy produces hypoglycaemic effect in proportion to the dosage given but the effect of sulphonylurea in therapeutic dosage resembles blood sugar regulation as in a normal person, hence chances of hypoglycaemia are remote. Unlike insulin therapy the effect of this drug persists for a few days even after its withdrawal. Creutzfeldt and Finter<sup>19</sup> giving a very high dosage to rabbits noted hypoglycaemia particularly if the animals were fasting. The symptoms could be readily relieved with intravenous injection of glucose. Clinical results of 781 diabetics compiled by Mohnike and Stotter<sup>16</sup> showed no confirmed case of hypoglycaemia.

The action of these drugs on the fat metabolism as indirectly observed by the formation of acetone bodies in the blood was studied in 17 subjects<sup>48</sup>. In 8 subjects who responded to sulphonylurea there was no increase of acetone bodies, hence those who respond are not likely to get diabetic ketosis. In therapeutic trials of diabetics with good results to tolbutamide, the blood lipids decreased<sup>12</sup>. This being the case, we should not be too much concerned in a diabetic developing cardiovascular accidents as lowering of blood lipids may diminish the chances of thrombosis.

In animals given radioactive tolbutamide the peak level was reached within 3 hours of its administration.<sup>6</sup> It is excreted in the urine to the extent of 90 per cent in three days and is not stored in any organ.

**Mode of Action:** The site of action of sulphonylurea has not yet been established. Considerable work has been done on (1) the pancreas—(a) alpha cells, (b) beta cells, (2) other endocrine organs, (3) insulinase and (4) liver enzyme.



**Pancreas.**—That the pancreas is necessary in some way has been generally accepted. This is proved by the following facts :

(a) The drug stimulates secretion of insulin from the islet cells<sup>34, 35, 17</sup> as injection of the drug in the pancreatic artery produces marked hypoglycaemia but not when injected into the femoral vein.

(b) In depancreatized dogs the drug was ineffective.

(c) Alloxan progressively destroys only the beta cells of the pancreas preserving the alpha cells. If the pancreas is only partially destroyed by alloxan, sulphonylureas can still act and lower the blood sugar. If the pancreas is completely destroyed by alloxan then these drugs do not lower the blood sugar<sup>5, 20</sup>.

(d) Wrenshall and Best<sup>52</sup> studied the amount of extractable insulin from pancreas at autopsy and tried to correlate it with the type of diabetics who respond to sulphonylurea. They found that the pancreas of the young diabetics showed lack of insulin and in clinical practice also they do not respond to sulphonylurea. Adult diabetics whose pancreas shows appreciable amount of insulin at autopsy would respond well to these drugs.

Insulin inhibits ketosis, enhances peripheral utilisation of glucose, increases glycogen content of the muscles and raises the blood pyruvate level. It is not yet clear whether sulphonylurea has similar effects as data of different investigators are conflicting.

**Alpha Cells :** The islets of Langerhans contain the alpha and the beta cells. It is generally assumed, though not finally proved, that alpha cells produce glucagon which is responsible for raising the blood sugar level. However, Best<sup>41</sup> has observed that we are still in the dark regarding the physiological role of glucagon.

Early German workers<sup>25, 9</sup> speculated that the effect of sulphonylurea in man was due to depression of the alpha cells, therefore, the beta cells producing insulin had a prepondering role, thus reducing the blood sugar.

If sulphonylurea is given to rabbits for one or two days there is no change in the pancreas but after a prolonged administration atrophy of the alpha cells was found while the beta cells showed only loss of granules suggesting a resting state<sup>19</sup>. On the other hand Volk et al<sup>51</sup> found no action on the alpha cells of the rabbits with tolbutamide.

The best proof whether the alpha cells are affected by sulphonylurea should be forthcoming from the histological examination of the pancreas in persons who died during treatment with the drug. No histological lesion of the alpha cells was found in diabetics who had died during treatment with sulphonylurea<sup>18, 24</sup>.

We can therefore conclude that the hypothesis of early German workers that sulphonylureas act by depressing the alpha cells and thereby reducing glucagon secretion is erroneous,<sup>24</sup> as there is neither good experimental nor post-mortem evidence to support the thesis.

**Beta Cells :** As stated above, the functioning pancreatic tissue is necessary for the action of sulphonylurea but the alpha cells have no part to play. The animal experiments<sup>26</sup> and post-mortem studies<sup>19, 52</sup> suggest that the beta cells are necessary for the action of sulphonylurea.

Alloxan in an experimental animal at first increases secretion of insulin by stimulating the beta cells but later the cells are exhausted resulting in permanent diabetes. As sulphonylurea stimulates the beta cells, it is feared that continuous use of this drug may result in permanent exhaustion of a partially functioning pancreas<sup>20, 40</sup>. If administered to children a permanent exhaustion of the beta cells is expected<sup>40</sup>.

**Other Endocrine Glands.**—(a) *Thyroid and the Adrenal Glands:* They have been studied as they can raise the blood sugar and therefore their action is antagonistic to that of insulin. The uptake of radioactive iodine diminished after administration of sulphonylurea<sup>29, 38</sup>. This effect is twice as high with carbutamide as with tolbutamide. However, there is yet no direct evidence to show that the decrease in the blood sugar seen in a diabetic is due to the depression of the thyroid gland.

(b) *Adrenal Gland :* The hypoglycaemic effect of sulphonylurea is more pronounced when the adrenals are removed<sup>30</sup>. Administration of cortisone and prednisone has no influence on the action of tolbutamide<sup>50</sup>. The 17-ketosteroids output is also not changed during the administration of tolbutamide. It is therefore generally accepted that sulphonylurea does not depress the adrenals.



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(c) *Pituitary* : There is prolongation of hypoglycaemic effect in hypophysectomised rats<sup>30</sup>.

**Insulinase.**—Mirsky and Broh-Kahn<sup>39</sup> have shown that insulinase, a proteolytic enzyme present in the mammalian liver, destroys insulin. A relationship between secretion of insulin and insulinase has been postulated<sup>13</sup>. Suggestions, therefore, have been made that diabetes is due to an increase in insulinase and sulphonylurea may be acting by destroying insulinase. Fritz et al<sup>26</sup> have demonstrated that carbutamide in normal dogs would decrease the blood sugar but not in a depancreatized dog treated with constant infusion of insulin hence action of sulphonylurea does not appear to be due to destruction of insulinase.

**Liver Enzyme.**—Liver is the key organ in the carbohydrate metabolism hence it is studied for the role it plays in the action of sulphonylurea. Liver slices in rabbits show inhibition of glucose production by tolbutamide<sup>8</sup>. There is evidence to suggest that action of sulphonylurea is by inhibition of release of glucose<sup>41, 45</sup>. Ten minutes after the administration of tolbutamide the glucose level in hepatic vein drops by 33 per cent<sup>3</sup>. Glucagon removes this trend—therefore action of tolbutamide takes place proximally to the phosphorylase system and thus inhibits glucogenolysis in the liver. While insulin promotes utilisation of sugar in the muscles, sulphonylurea directs the flow of sugar into the liver<sup>7</sup>.

The above evidence suggests that the action of sulphonylurea may be in inhibiting the formation of glucose from glycogen in the liver.

**Dosage** : The dosage of either carbutamide (BZ-55) or tolbutamide (D 860) is about the same. Recommended dose is two tablets (0.5 g each) three times a day for two days (but initial dose of two tablets twice a day is also effective)<sup>4</sup>, then two tablets twice a day for the next two days and then the maintenance dose. A majority require maintenance dosage of two to three tablets a day. A few require only one tablet a day. While carbutamide could be given as a single dose, tolbutamide has to be given into two divided doses for an uniform 24-hour action.

**Age** : These drugs are found very effective in elderly diabetics<sup>16</sup>. Eighty per cent of cases whose diabetes is discovered after the age of 50 are likely to respond.

In juvenile group of diabetics they are found ineffective<sup>21, 9, 15</sup>. Kinsell et al<sup>33</sup> on the other hand found them to be effective in some juvenile diabetics. These variations in the observations are not surprising if the mode of action is through the functioning beta cells of the pancreas. Whether the drug could be effective could be determined by therapeutic trials only.

When less than 40 units of insulin is required to control the diabetes, response to sulphonylurea is probable<sup>16</sup>. If sulphonylurea is given with insulin, then insulin requirement is appreciably reduced<sup>46</sup>.

Whether it is desirable to give drug alone or with insulin is disputable. We feel that where insulin requirement is very high and sulphonylurea only partially controls the diabetes then insulin may be supplemented, only if by this the cost is reduced. If the cost is of no consequence and if sulphonylurea fails, insulin alone should be given.

**Habitus** : Thin diabetics do not respond<sup>22</sup> while the obese type are more likely to respond<sup>9</sup>. Antia and Phatak<sup>4</sup> found encouraging results with the overweight patients as with the patients with an average weight and they ascribe this to the lower calories consumed by the hospital class of Indian patients as compared to those in the Western countries.

**Diet** : The role of diet in diabetes is not well appreciated. A diabetic always dreads the idea of observing a diet.

In clinical practice it is seen that an obese diabetic has a good chance of having his diabetes controlled and even the sugar tolerance curve brought to normal if his weight is reduced to the ideal body weight. For this reason neither sulphonylurea nor insulin is necessary in uncomplicated obese diabetics, till the body weight is reduced to ideal body weight, by a reducing diet.

Since beta cell exhaustion is feared with long continued treatment, it is best not to give the drug in uncomplicated obese diabetic till the body weight is reduced.

During the treatment with these drugs, unless the calorie intake is regulated the diabetes may not come under control<sup>4, 6</sup>.

**Duration of Diabetes** : The duration of time that lapses between the diagnosis of diabetes and beginning of sulphonylurea treatment has a bearing on the response. Of those recently diagnosed, 98 per cent respond but those who were not diagnosed for more than 10 years, 60

per cent respond<sup>9</sup>. However, in some clinics<sup>16</sup> no pronounced difference in the length of history and response to drug was noted.

**Complications of Diabetes :** Unlike insulin the action of sulphonylurea is not immediate. Besides, the drug cannot be relied upon to act in all cases as it is not a substitution therapy, the action depending upon functioning pancreatic tissue. These drugs are therefore not advocated during an emergency treatment like diabetic coma. They should not be used for diabetes with complications like retinopathy<sup>16</sup>, as also in pregnant diabetic women and when surgical intervention is contemplated.

**Carbutamide and Tolbutamide :** There was no difference in efficacy of both these drugs as tried in 60 patients in German clinics<sup>16</sup>. These drugs do not damage the kidney. Albuminuria had been reported by some clinics but it was soon found that the tests done with sulphosalicylic acid and picric acid were positive with excretory products of tolbutamide and are not due to proteinuria. Constipation has been noted<sup>16</sup>. No deleterious effects were noted on the bone marrow and the circulating cells<sup>19</sup>.

Liver function impairment and jaundice with tolbutamide are recorded<sup>16, 47</sup>. On the other hand no deterioration in liver function was noticed even among those whose liver function was originally impaired.

Hypoglycaemic reactions are very uncommon but have been noted by Gastineau<sup>27</sup> who had followed a higher dosage schedule.

Colwell et al<sup>17</sup> have summarised complications in 7,000 patients as severe hematological, hepatic and general allergic reactions in 2 per cent while milder side effects as rash, gastrointestinal symptoms, etc. in additional 3 per cent.

Carbutamide has been found to be more toxic than tolbutamide. The former has been withdrawn from clinical use in the United States. Tolbutamide, however, has been accepted as a safer drug.

**Conclusions.**—The sulphonylureas have not only opened an era of oral treatment for diabetes but also an alternative drug in insulin-sensitive patients. They have also stimulated a great deal of research in the basic understanding of diabetes.

These drugs appear to act either by stimulating the beta cells of the pancreas to release insulin or inhibit the release of glucose by the liver. It is feared by some that long continued administration may exhaust the beta cells.

The initial dosage required is 4 to 6 tablets a day. The maintenance dosage is two to three tablets. Tolbutamide be given in two divided doses. Tolbutamide is accepted to be safer than carbutamide.

The drug acts best in those who have functioning pancreatic tissue as in obese elderly recent diabetics. It is not so effective in young and thin diabetics or diabetics of over 10 years' standing.

The drug is not advocated in obese diabetics as Colwell et al<sup>17</sup> have observed, "The diabetics likely to respond best are those who need insulin least". Ideally an uncomplicated obese diabetic should be reduced to normal body weight before starting with these drugs. Even during the therapy if the intake of total calories is not regulated the response is poor.

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## AORTOPULMONARY FISTULA

D. Jaganatha Reddy

Bharadwaj et al record clinicopathological findings in a case of aortopulmonary fistula. A male aged 32 years was suffering from orthopnoea of three days' duration. The mediastinum was found shifted to the left and on paracentesis thoracis on the right side 400 c. cm of haemorrhagic fluid was removed. The patient expired 6 hours later. At autopsy, significant changes were confined to the ascending aorta, corresponding portion of the pulmonary artery and the lungs. Both gross and microscopically the aorta and the pulmonary vessel showed changes typical of syphilis. In addition, the pulmonary artery was adherent to the aorta and communicated with the aorta through a rent of three mm in diameter. Kahn test of blood was positive.

Both the pleural cavities contained considerable amount of blood-stained fluid. The lungs were collapsed. There was interstitial oedema of the lungs. The fluid in the pleural cavities contained red blood cells, lymphocytes and 2.8 mg per cent protein. The solitary accumulation of fluid in the pleural cavities and the presence of normal quantity of fluid in the pericardial cavity, were thought by the authors as due to sudden changes in the systemic pressure causing an outpouring of interstitial fluid. They further suggest that the increase in pulmonary pressure in their case resulted in pleural exudation, since pleural capillaries drain into the pulmonary vein. Shift of the mediastinum to the left as observed in their case was due to collection of exudate on the right side initially. This case report should stimulate further study of pulmonary haemodynamics.

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## ARTHRITIS, RHEUMATOID

M. M. Desai

**Incidence:** Though cases of rheumatoid arthritis often come for medical attention to our hospitals and in private practice, it has been the general impression that the incidence of this disease is not so high in this country as in some of the Western countries. In a leading business house in Bombay, with an average monthly staff of 1200 on its payroll, observations for rheumatic diseases were carried out by me for four years. The ages of the staff members varied from 18 to 56 years, the majority of them belonging to the age group of 20 to 40 years. During this four-year period, I came across only a single case of rheumatoid arthritis in a patient 50 years old (and three cases of osteoarthritis, three cases of slipped disc and not a single case of gout or other forms of arthritis). From the experience of other colleagues serving as physicians to commercial establishments or industries, I have gathered that the occurrence of rheumatoid arthritis has not been a problem, particularly in the loss of important man-hours.

It has been estimated that 700,000 cases of rheumatoid arthritis exist in the U.S.A. (Stecher et al, 1953).

**Aetiology:** The aetiology of this disease is still obscure and efforts have been made to ascertain it in several experimental studies. Levinsky and Lansbury (1951) failed to transmit rheumatoid arthritis to human beings by the direct passage of synovial fluid from rheumatoid cases. The role of focal infection in rheumatoid arthritis has come to be relegated in background and this has been the observation of numerous workers (Bjerrum, 1952; Dietz, 1952).

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Rapport et al (1951) brought an interesting observation to light. They came across four cases of rheumatoid arthritis which were thought to be the result of chronic intestinal amoebiasis. Rinehart (1952) found the presence of *E. histolytica* in the stool of 92 of 101 consecutive patients of rheumatoid arthritis and suggested an aetiological relationship between these two conditions. The incidence of amoebic infection in this latter series is too high to be ignored and cannot be considered as fortuitous. The incidence of chronic intestinal amoebiasis in India is fairly high and it is worth investigating whether any relationship does exist between intestinal amoebiasis and rheumatoid arthritis. Until more reports are forthcoming on this subject, one has to look at this observation with some circumspection.

*Clinical aspects:* This disease is more common in elderly patients but younger age groups are not exempt. Cecil and Kammerer observed 100 consecutive patients in whom the disease appeared at or after 60 years of age. K. K. Sikka (Cur. Med. Practice, June, 1958) observed 100 consecutive cases of rheumatoid arthritis at the Gandhi Memorial and Associated Hospitals in Lucknow and reported that the age incidence of patients when they first came for examination was up to 20 years—18 cases, 21-40 years—68 cases, 41-60 years—14 cases. The youngest patient was a male aged nine years and the oldest was a female patient of 50 years. The average age of the patients at the time of first examination in Sikka's series was 27.9 years for male and 32.9 years for female. The author states that these figures do not correspond to those of the incidence usually quoted in literature.

Of the 100 cases observed by Cecil and Kammerer, 50 were male and 50 female; in Sikka's series, there were 60 male and 40 female patients. Probably, the higher incidence observed by this author in male patients was due to the fact that larger number of male patients seek medical attention in our public hospitals than female. Davidson et al (quoted by Sikka) observed 532 patients and found that the incidence of rheumatoid arthritis was in the ratio of 100 males to 162 females. Majority of authors have observed a higher incidence of rheumatoid arthritis in female patients as compared to male patients. Jonsson (1953), Kelly (1952) and Parr (1951) have described the onset of this disease as often acute, asymmetrical and occasionally mono-articular in patients at any age. Edstorm (1952), Kelly (1952) and Parr (1951) have stated that patients frequently get onset of symptoms from an injury at the affected joints and this has led these authors to cite trauma as an important precipitating factor. Robinson et al have remarked that rheumatoid arthritis is a capricious disease and can have almost any type of onset. Vainio and Oka (1953) observed that ulnar deviation of the fingers was more frequently seen in female patients and Lush (1952) observed that this common type of deformity in rheumatoid arthritis was more common in patients with long duration of the illness. Lush also observed that occupation did not have any bearing on the incidence of this form of deformity. Many authors have observed that ulnar deviation of the fingers is a result of certain anatomical alterations, e.g., atrophy of the muscles of the hand, swelling of periarticular structures, and laxity of collateral ligaments (Rose and Wallace, 1952; Snorrason, 1951; and Lush, 1952).

Extra-articular manifestations of the skin, tendons, tendon sheaths and muscles have been noted by various authors (Schoch, 1952; Kestler, 1952; Mueller and Mead, 1952).

*Pathological aspects:* H. J. Gibson emphasized the widespread distribution of the pathological changes of rheumatoid arthritis in the mesenchymal tissue. The lesions were characterised as pleomorphic and presenting three important features namely, granulation tissue followed by an overgrowth of collagen tissue, fibrinoid degeneration followed by liquefaction and cavitation, and chronic inflammatory changes with infiltration mainly by round cells and plasma cells, polymorphonuclear leucocytes and histiocytes. The granulomatous lesion has been considered non-specific, but its fairly constant presence in joints, subcutaneous tissue and muscle gives a fairly characteristic picture of the pathology of this disease.

The subcutaneous nodule of rheumatoid arthritis has a central avascular area of necrosis and the morphological picture has been reviewed by Gibson (1951) and Hunt and Blanchard (1951). Lesions identical to the subcutaneous nodules were described in synovial tissues by Gibson. In the articular and periarticular tissues, infiltration with round cells was observed and in the synovial villi, accumulations of lymphocytes and plasma cells formed the so-called Allison-Ghormley foci. However, Gibson and Shafer and Larmon emphasized that such pathological alterations were not specific for rheumatoid arthritis.

Gibson also described the pathological changes in bones which occurred simultaneously with those in the synovial membrane and included round cell infiltration and fibrosis of the epiphy-

seal marrow. There may be resorption of bone near the affected area which on radiological examination is seen as marginal erosion and cyst formation. The voluntary muscles of patients with rheumatoid arthritis showed changes of atrophy and degeneration, and probably they could be explained as due to disuse atrophy of the muscles (Traut and Campione, 1952). Sokoloff (1953) studied 105 cases of rheumatoid arthritis at post-mortem examination and reported an incidence of rheumatic heart disease in this group of 11.5 per cent, whereas, the incidence of rheumatic heart disease in control group of 1154 consecutive post-mortem was only 5.7 per cent. It is suggested by him that the occurrence in rheumatoid arthritis of organic heart disease which is indistinguishable from rheumatic heart disease is more than a coincidence.

**Laboratory Investigations:** Jeffery (1952, 1953) studied more than 200 patients suffering from rheumatoid arthritis and observed that the anaemia is of hypochromic and normocytic in type; he also observed that the volume of red cells was low giving rise to a reduction of total blood volume; there was reduction in serum iron. Ogryzlo (1953) described the presence of lupus erythematosus (L.E.) cells in patients with severe form of this disease.

An increase in the E.S.R. has been found to closely follow the severity of the disease except in those cases where there was a marked increase in the serum globulin and severe anaemia. (Fletcher, 1952). Goldberg et al (1952) observed that in assessing the activity of rheumatic process, the Westergren method was more reliable than the method of Wintrobe of determining the sedimentation rate. Electrophoretic studies of serum proteins showed in a number of studies increase in globulin concentrations (Lovgren, 1953, etc.).

**Acute Phase Reactants.** A number of tests have come into existence which depend on the appearance of some abnormal constituents, sometimes in abnormal quantities, during the active stages of diseases with a generalised inflammatory process. They are ill-understood on theoretical grounds, but several of them have been popular in the States.

The C-reactive protein test is positive during the active stages of rheumatoid arthritis and diminished or absent during spontaneous or cortisone-induced remissions. It has been suggested as a more dependable test of rheumatoid activity than the E. S. R.

**Radiological Findings:** Fletcher and Rowley (1952) have described the radiological features of rheumatoid arthritis following a survey of routine films in 200 cases of rheumatoid arthritis. They also made use of a special magnification technique. These authors detected at least one radiological abnormality within three to six months of onset of the disease. Some mild cases did not show any radiological changes for even two to three years. In three-fourth of the cases, there was erosion of the bones and reduction in the joint space of the affected joints; there was osteoporosis in 64 per cent of the examinations. The authors state that alteration of joint space and osteoporosis were the earliest features on radiological examination.

It is interesting to state here that these authors observed that the joints most commonly affected were the metatarsophalangeal, particularly the fifth. Next in order, the second and third metacarpophalangeal joints were more often involved. Osteoporosis should not be taken as an important diagnostic feature as it may be seen in many other conditions.

**Treatment: Pyrazole Derivatives.** Phenylbutazone (available in India as butazolidin) and Irgapyrin (which is a combination of butazolidin and amidopyrine), have been extensively used for the treatment of rheumatoid arthritis in India. A large number of physicians (personal communications) have observed very good relief in the condition of rheumatoid patients with the use of Irgapyrin which has been the more commonly used drug of the two in this country. Both these preparations are more effective in acute cases as compared to chronic cases, though even in the latter satisfactory results are observed.

Butazolidin and Irgapyrin are not merely analgesics but it has been found from experimental and clinical observations that they have a definite anti-inflammatory effect which is different from that of the hormonal preparations. Reports on the use of these pyrazoles in rheumatoid arthritis have not been published in India but a large amount of world literature has gathered round the use of these drugs. Improvement in both subjective and objective manifestations of rheumatoid arthritis with phenylbutazone has been reported by a number of authors (Kuzell and Schaffarzick, 1952, 1952, 1953; Byron and Orenstein, 1953; Smith and Kunz 1952; Steinbrocker et al, 1952; Stephens, et al, 1952). Control studies with the use of phenylbutazone and identically prepared placebos have yielded very convincing results. There is relief from pain, increased mobility of the joints involved, and reduction in the size of the swelling. Various

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authors have observed varying percentages of significant improvement (i.e. grades I and II remissions according to therapeutic criteria established by the American Rheumatism Association). Steinbrocker et al, reported major improvement in 23 per cent of their patients, Kuzell et al, in 59 per cent and Byron and Orenstein reported in 92.5 per cent improvement in 40 patients followed up by them.

Recently, Fjellstrom et al (1957) carried out a methodological and controlled clinical trial in 82 cases of rheumatoid arthritis at the Boden Central County Hospital, Sweden. It was one of the aims of this investigation to exemplify procedures practicable for clinical observation of drugs useful in rheumatoid arthritis. The drug tested here was phenylbutazone. A daily dose of 800 mg was given initially for four days which was reduced during the next three to four days to 600 mg per day and finally, a maintenance dose of 300 to 400 mg a day was administered. The treatment was carried out by a "double blind" method in two groups, one receiving phenylbutazone and the other placebos. The therapeutic response and improvement in functional capacity were judged according to the criteria of the American Rheumatism Association. The authors state that the response of the rheumatoid activity to the treatment given during their observation in the hospital was significantly better in patients treated with phenylbutazone compared to the controls. There was no effect on the E.S.R., pulse rate and total and differential white cell count. The range of movement of the joints involved was better after treatment with phenylbutazone than among the controls. Side effects were observed in a few cases, the most common complaint being nausea.

Barcelo and Serra Perralba (1957) treated 110 patients of rheumatoid arthritis with a combination of butazolidin (200-400 mg daily) and prednisone, 5 mg daily. Not only that they observed very good results, but they also noticed that in most patients the addition of 5 mg of prednisolone permitted control of symptoms with 200 mg of butazolidin, instead of the usual dose of 400-600 mg daily. Moreover, patients who formerly required 15 mg of prednisone daily, required a smaller dose of it when thus combined with butazolidin. The incidence of side reactions of either drug was also minimised to a large extent (Paper read at the IX International Congress on Rheumatic Diseases at Toronto).

Various toxic reactions have been reported both with phenylbutazone and Irgapyrin, and necessary amount of care is required in the selection of patients, the route of administration, and the daily dose. Patients with an antecedent history of peptic ulcer or those with an active peptic ulcer should be carefully excluded from treatment, as gastro-intestinal haemorrhage and perforation have been reported by many authors (Granirer, 1952; Stephens et al, 1952; Cudkowiec and Jacobs, 1953; Krainin, 1953; Kuzell et al, 1953). As all pyrazole derivatives have a tendency to lower the total white cell count, it is always necessary to keep a watch on the total and differential white cell count during treatment with both phenylbutazone and Irgapyrin. Cases of agranulocytosis have been reported in the Western countries but such reports have not been met with in the medical literature in this country. However, during treatment with these drugs, the patients should be instructed to report immediately if untoward manifestations like stomatitis, sore throat, drug rash or oedema of the feet make appearance. Toxic reactions with phenylbutazone have been reported as being more frequent in females (Kuzell, 1953) and for this reason, more care should be given in selecting female patients for treatment.

Both phenylbutazone and Irgapyrin though they give good results in rheumatoid arthritis, are not really curative in nature. Taking advantage of the relief from pain, reduction in swelling and a sense of confidence instilled in the patient by such results, one should supplement the treatment with suitable rehabilitation therapy.

I would like to add here from experience that when these pyrazole preparations are administered intramuscularly, the maximum care should be taken in the technique of injection, or else unfavourable local reactions are likely to arise. This may be in the nature of pain and induration, but if the injection is made deeply in the thick mass of the gluteal muscles, and given at a slow rate, one could definitely minimise such unfavourable reactions.

Steroid Hormones. Cortisone, hydrocortisone and corticotrophin (ACTH) have been extensively used in several countries for the treatment of rheumatoid arthritis. Recently, prednisone and prednisolone have to a large extent replaced the use of the steroids which were used a few years ago. A vast amount of literature has accumulated on the use of these hormones, which on the one hand have been dubbed as "glorified aspirin" and on the other as very effective and potential remedies. A balanced and careful judgment is required and it would



be some more years to obtain a definite and crystallised view on the subject of the steroid hormones. The reports are too numerous to be reviewed here but certain essential features of hormone therapy would be stressed.

With the use of the adrenal hormones, subjective and/or functional improvement has been more significant than the objective (Clark et al, 1953). At the Mayo Clinic, symptomatic improvement was observed in 99 out of 100 patients. Relapses after cessation of treatment have been often observed which suggests that this treatment does not influence the ultimate course of the disease. Following the administration of these hormones, a reduction of the joint swelling, improvement in the contractures and normalisation of temperature have been observed. There has been some improvement in some of the non-arthritic changes such as enlargement of the lymph nodes, subcutaneous nodules, presence of pericarditis, etc. Very chronic contractures are not affected with the use of hormones.

Spence (1958) has recommended an initial dose of 100 mg of cortisone daily for a week, which is gradually reduced to 50 mg daily. A maintenance dose is usually necessary and the requirement for this would depend on the severity of the disease and the response of the individual (Hench, 1952). Larger doses are better tolerated by men than women (Glyn, 1957). Some authors recommend that during prolonged cortisone therapy, ACTH should be administered on three or four days in a month, thus combining the advantages of both and minimizing their disadvantages (Glyn, 1957).

Glyn (1957) has divided the contra-indications to the hormones, cortisone and ACTH as, (1) *absolute contra-indications*, viz. active or recently active tuberculosis, total failure to respond and cases with pre-existing irreversible joint damage; (2) *major, but relative contra-indications* such as peptic ulcer, psychosis, diabetes mellitus, generalised osteoporosis, significant epilepsy, etc.; (3) *minor* ones like cardiovascular or renal insufficiency, severe degree of hypertension, etc.

**Prednisone and Prednisolone.** Prednisone and Prednisolone were developed by Herzog and co-workers in 1954. In India, these two compounds have been available only recently and not many reports as to their use in rheumatoid arthritis have seen the light of publication. On account of certain drawbacks of cortisone and hydrocortisone, efforts were made by pharmaceutical chemists to alter the chemical structure of cortisone so as to do away with many of their undesirable effects and to develop compounds which would be therapeutically more potent. Prednisone and prednisolone are therapeutically more potent on a weight for weight basis, compared to cortisone and hydrocortisone. On an average, the potency of prednisone per mg has been found to be approximately four times that of hydrocortisone. Between the two, these compounds have very little difference as regards their therapeutic potency, again on a weight for weight basis. With the use of prednisone and prednisolone, the incidence of fluid retention, blood pressure elevation and changes in the electrolyte balance of the body are definitely reduced, but the incidence of digestive symptoms, purpuric haemorrhages and "hot flushes" became high. Boland (1957) reports from his own experience and that of Margolis et al and Dubois that the frequency of ulcer-like symptoms and other digestive complaints, accompanied by or without the presence of peptic ulcer, are complications which have a higher incidence with these new analogues. Boland (1957) reports that out of 109 patients undergoing treatment with hydrocortisone, only seven cases had symptoms characteristic of peptic ulcer, whereas 33 patients experienced such after prednisone or prednisolone therapy was substituted; radiological examination showed that out of these 33 patients, 8 had peptic ulcer. Three of these patients had haematemesis, but no case of perforation was observed. These observations suggest that prednisone and prednisolone should not be used indiscriminately.

Boland (1957) treated 250 patients with adrenal hormones for a period of two years of whom 141 were critically studied during continuous treatment for periods varying from six to nine months. The pattern of improvement resulting from suppressive doses of the different hormones (cortisone, hydrocortisone, prednisone and prednisolone) was practically similar. The treatment plan was comprising of three stages namely, initial administration of suppressive doses, gradual reduction of the dosage, and finally, continuous administration of maintenance doses. It has been suggested by Boland that efforts should be made to avoid very rapid and dramatic improvement with high doses in the beginning as he feels that long range results are better. He recommends 15 to 20 mg of the newer analogues daily for severe cases, 12.5 to 15 mg for moderately severe cases, and 10 to 12.5 mg for moderate cases. Such doses should be continued until



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satisfactory suppression of the symptoms is achieved, ordinarily for one to three weeks. The maintenance dose should be the smallest daily amount which would sustain satisfactory control of the symptoms.

For initial treatment of rheumatoid arthritis, there is little difference noted with either prednisone, prednisolone, cortisone or hydrocortisone. Patients already receiving hydrocortisone can be satisfactorily switched over to the newer analogues, if appropriate doses are administered.

Based on his experience, Boland suggests the following criteria for selection between hydrocortisone or prednisone and prednisolone for the treatment of rheumatoid arthritis. It should be advisable to commence treatment with hydrocortisone as it is less likely to produce gastric upsets; if improvement is diminishing, one may change over to the newer steroids. If there is potential danger of fluid retention as in congestive cardiac failure, hypertension or in cases who develop oedema following hydrocortisone, prednisone and prednisolone would be the drugs of choice. Patients who have not responded well to cortisone or hydrocortisone may be given a trial with prednisone or prednisolone. On the other hand, in patients with a past history of peptic ulcer or gastro-intestinal upsets, one should give preference to hydrocortisone.

**Other Lines of Treatment.** Crain and Tillis and Connacher stated that addition of calcium succinate to aspirin did not have any advantage over the mere use of the latter drug. Para-aminobenzoic acid could increase the blood level of sodium salicylate when given with the latter drug. Batterman et al (1951) observed that sodium gentisate had nearly the same therapeutic potency as aspirin.

After several years of gold therapy, it has not yet been possible to decide whether gold salts have any real value in the treatment of rheumatoid arthritis. With the advent of phenylbutazone and the steroid hormones, gold salts have been relegated into the background, but still there is a school of thought which believes in the therapeutic value of this compound. The golden rule should be to make use of these salts only when therapy with phenylbutazone or the steroids has failed, or in those cases where these compounds are contra-indicated, though it is possible that cases which are contra-indications to phenylbutazone and the steroids would probably also require to be excluded from treatment with these salts. Treatment with gold salts has also been recommended during intervals between courses of phenylbutazone or the steroids.

**General Considerations on the Treatment of Rheumatoid Arthritis.** It often happens that patients with rheumatoid arthritis are considered as chronic, incurable cases with a relentlessly progressive disease and for whom very little could be achieved by way of treatment. No doubt that this disease is one of the difficult problems met with by a clinician, but with appropriate selection of drugs and supplementary measures, particularly rehabilitation, much can be achieved with satisfaction of the physician and the patient alike. A properly planned treatment programme can go a long way to help the patient obtain relief from his prolonged suffering.

The objects of treatment are--

1. To relieve the patient from his symptoms, particularly the pain and swelling and thus make him comfortable,
2. To suppress the course of the disease,
3. To avoid the formation of contractures and deformities,
4. To prevent complications, and
5. To rehabilitate so that the patient can, as far as possible, lead a useful existence.
6. Patients' general condition and nutrition (adequate calories, vitamins and mineral supplements) should be attended to and in some cases, psychotherapeutic measures may be required.

Taking advantage of the relief from pain and joint swellings which is possible to obtain with phenylbutazone or the steroids, one should institute a well-conceived plan of rehabilitation treatment. At the Rehabilitation and Training Project, Bombay, M.V. Sant (personal communication) has been able to carry out successfully rehabilitation treatment of patients of rheumatoid arthritis with simultaneous use of Irgapyrin, administered orally. Initially, suppressive doses are administered, and later on, maintenance doses for prolonged periods.

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## ATHEROSCLEROSIS, PATHOGENESIS AND PREVENTION

P. L. Wahi

In the last decade clinical, pathological and electrocardiographic studies have disproved the fatalistic assumption that coronary atherosclerosis is an inevitable component of aging<sup>1</sup>. It is argued that atherosclerosis is a disease process due to certain physico-chemical changes associated with lipid and cholesterol metabolism. Such a view is the result of innumerable studies on the morphology and pathological chemistry of atherosclerotic lesions besides the experimental production of atherosclerosis with cholesterol-feeding experiments. Though validity of application of some of these experimental findings to human beings has been questioned yet it is fairly clear that a long term observation of cholesterol levels in patients with coronary disease especially after heavy fatty meals, against controls, shows that cholesterol is an important culprit<sup>2</sup>. Moreton (1950)<sup>3</sup> suggested that numerous fatty meals produce showers of large lipid particles in the blood (chylomicrons) which are deposited in the arterial intima. The neutral fats and fatty acids are reabsorbed by macrophages but the large lipid particles are not and lead to atheroma. Further studies in this direction revealed that plasma cholesterol-phospholipid ratio and concentration of lipoproteins of specific size determined by ultracentrifuge (Sf<sub>12</sub>-Sf<sub>200</sub>) are more important than total serum cholesterol. Variations in the plasma cholesterol-phospholipid ratio may precipitate cholesterol in arterial intima. This assumption was supported by the injection of surface active agents, such as detergents Tween 80 and Triton 20 into cholesterol-fed rabbits leading to significant elevation of the serum phospholipid and reduction in atherogenesis<sup>4,5</sup>. Chelating agents like EDTA, and hydralazine also cause a prompt fall in plasma cholesterol in man<sup>6</sup>. Heparin has important role in clearing post-prandial lipaemia in experimental dogs by forming a heparin-phospholipid complex, clearing up alimentary lipaemia, reducing lipoproteins and Sf 10-50 lipoprotein aggregates. This line of thought has led to the counting of mast cells in atherosclerotics and in pre-and post-menopausal women, because heparin is produced by mast cells<sup>7,8</sup>. It was also demonstrated that this post-prandial lipaemia is less in the manual labourers thus explaining the relatively low incidence of atherosclerosis in this class of individuals<sup>9</sup>.

Dietary intake of cholesterol as such appears relatively insignificant in atherogenesis as there is a larger synthesis of cholesterol in the body but fat consumption, especially with fats with large component of saturated fatty acids, is found to increase the incidence of atherosclerosis<sup>10,11,12</sup>. This has led to the study of racial incidence of atheroma and dietary habits of various nations. Yudkin (1957)<sup>13</sup> has shown that in most countries correlation between intake of dietary fat and incidence of coronary atherosclerosis is apparently significant but it is only true upto the figure of 120 g daily intake of fat. Ancel Keys<sup>10</sup> and his co-workers have studied in detail the diet habits and serum cholesterol levels in men of varying ages and physical activity and belonging to various nationalities. They came from places like Minnesota, Sweden, Naples and South Africa. It was noted that heavy manual labourers had relatively lower levels of cholesterol than sedentary people but it was much less significant when compared to the effect of habitual high fat diet on the total cholesterol and Sf lipoproteins. It is claimed that the ingestion of fats containing major portion of unsaturated fatty acids or vegetable oils reduces the serum cholesterol, and that consumption of fats with saturated fatty acids is a factor in the causation of atherosclerosis<sup>15,16</sup>. A strange note is sounded by Sinclair<sup>17</sup> who thinks that hypercholesteremia is due to deficiency of essential fatty acids in the diet and consumption of corn oil, a fat rich in linoleic acid, can correct this.

Besides the dietary factors, the role of sex hormones, and the hormones of thyroid and adrenal cortex is not completely understood. Oestrogen can reduce the serum cholesterol, cholesterol-phospholipid ratio without changing the phospholipid levels in patients with previous myocardial infarction<sup>18,19</sup>. Similarly thyroid extract can cause lowering of serum lipo proteins and serum cholesterol<sup>20,21</sup> and tri-iodothyroacetic acid affects the euthyroid men with coronary infarction and high serum cholesterol levels in a similar fashion<sup>22</sup>.

The role of hypercholesteremia and fatty meals on the coagulation of the blood and the effect of hard manual labour in preventing such deleterious effect is attracting attention.

Though as yet there is no proven remedy to prevent atherosclerosis but there are various lines of thought that are being investigated. Weight reduction by low caloric diet, with or without any particular reduction of fat component of the diet, is considered quite a sound proposition. Reduction of cholesterol in diet is difficult and its final result in prevention of atherosclerosis

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is not proved. The low fat diet with emphasis on unsaturated fatty acids in the fat ingested is also recommended by some workers<sup>23</sup> though it needs further observation before a final decision can be taken<sup>24</sup>. Plant sterols (sitosterol) and substances like dihydrocholesterol which reduced the absorption of cholesterol and thus reduced serum cholesterol though promising<sup>25</sup>, have not as yet fully justified their routine clinical use. A critical analysis of various claims regarding the usefulness of lipotropic agents<sup>26</sup> in prevention of atherosclerosis indicates that these agents are quite ineffective. The value of heparin by subcutaneous route as suggested by Engleberg et al<sup>27</sup> is as yet unproven. The role of hormones like oestrogens or thyroid extract though also attracting attention is yet far from being conclusive. Detergents have been used in experimental atherosclerosis with encouraging results; their clinical use awaits a thorough trial<sup>6</sup>.

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## ATHEROSCLEROSIS, ROLE OF DIET IN

R. H. Dastur and F. P. Antia

Degeneration of the arteries starts in infants even 3 to 4 months old (Moon)<sup>1</sup> and gradually increases with advancing years. The sciences of nutrition and food technology have made considerable progress and it is now possible to manufacture foodstuffs like hydrogenated oils, degerminated cereals and concentrated vitamins and minerals. How far the administration of these refined foods and concentrated vitamins is responsible for the degenerative changes has not been definitely assessed and yet there exists a trend to produce these substances in higher concentrations.

The exact aetiology of atherosclerosis is not yet known. There appears to be a combination of factors, the most important of which is the hereditary predisposition. Other factors incriminated are diet, stress and strain of modern life, excessive smoking, alcohol, lack of exercise, diabetes, high blood pressure and hormonal influences. As it is feasible for a person to control his diet it is necessary to understand its role in the production of atherosclerosis.

The lesions of atheroma contain lipid material and hence research in the metabolism of lipids has been stimulated recently. Lipids exist in the blood as cholesterol, neutral fats and phospholipids. Recent trends suggest that the blood lipid level is regulated by (1) the total intake of calories, (2) cholesterol, (3) total fat, (4) type of fat, saturated and unsaturated, (5) essential fatty acids, (6) proteins, (7) carbohydrates and (8) vitamins.

**Total Calories :** Atherosclerosis is a disease of over-nutrition. It is usually seen in the obese who live well ; their blood cholesterol level is found to be higher than that of a lean person of corresponding age. Mann et al<sup>2</sup> gave a 6000 calorie diet with severe exercise and did not find rise in blood cholesterol or total lipids but as soon as exercise was stopped the weight and total lipids increased. Toor et al<sup>3</sup> studied early well settled Yemenite immigrants to Israel who because of a higher income consumed more calories and fat than the recent Yemenite immigrants of the same age and sex whose income was much less and hence consumed less calories and fat. Serum cholesterol and total lipid level were significantly higher in the early immigrants and their mortality from atherosclerosis was four times higher than that of the recent immigrants.

**Cholesterol** : Most attention on the study of atherosclerosis is focussed on cholesterol for two reasons: (a) cholesterol deposits are found in an atheromatous patch; (b) compared to other lipids, cholesterol can be easily estimated in the laboratory. As atheromatous lesions could be produced in animals like rabbits by feeding them with cholesterol it was assumed that cholesterol in the diet was primarily responsible for the high blood cholesterol and atheroma. Studies of Lewis et al<sup>4</sup> clearly show that cholesterol levels in men and women are about the same till the age of 20 and then there is a rise with age, more in men. Above the age of 50 the level is higher in women than men. Hildreth et al<sup>5</sup> showed that by keeping the total calories constant and restricting the cholesterol intake, the blood cholesterol level increased or decreased, corresponding to an increase or decrease in the ingestion of total fats. Hence factors other than ingested cholesterol were responsible for atherosclerosis. It has been pointed out<sup>6</sup> that just finding high blood cholesterol in coronary disease does not necessarily mean that cholesterol is the cause of the disease ; it may as well be the result of coronary artery disease.

**Sitosterol** : Sitosterol is a vegetable sterol (just as cholesterol is an animal sterol). Different varieties of sitosterols have been described. It is present in cotton seed, soyabean, etc. and is not absorbed from the digestive tract. Pollack demonstrated in 26 subjects that when 5 to 10 g of sitosterol was given daily in 3 divided doses with the usual diet for 8 days to 8 months, the blood cholesterol level was reduced, though continuous administration was necessary. Best et al<sup>8</sup> could also obtain reduction upto 20 per cent in the serum cholesterol level by administration of sitosterol. It is believed that sitosterol interacts not only with ingested cholesterol but also with cholesterol excreted in bile and forms unabsorbable compounds, thus preventing absorption of cholesterol from the gut and reducing serum cholesterol. Barber and Grant<sup>9</sup> gave sitosterol in the form of biscuits with gratifying results.

**Total Fats** : Kempner<sup>10</sup> was able to bring down blood cholesterol level by low fat diet. In the U.S.A., where over 40 per cent of total food calories are supplied by fat, the highest incidence of coronary disease exists. Whereas in Japan where fat supplies less than 10 per cent of the total calories, the incidence of coronary disease is low. Similarly during World War II when there was scarcity of fat in Europe, the incidence of coronary disease declined and it increased again when fats were easily available. Keys et al<sup>11</sup> and Hatch et al<sup>12</sup> have shown that it is the total fat content of the diet which regulates blood cholesterol level and not the total calories or cholesterol in the diet. Page et al<sup>13</sup> have commented that there is clinical and experimental evidence to correlate excessive intake of fat and atherosclerosis but other factors like obesity, exercise and total calorie intake have not been properly evaluated and hence a direct correlation between total fat and atheroma must be considered unresolved.

**Type of Fats** : Fats in the diet are compounds of fatty acids like stearic, palmitic and oleic with glycerol. The fatty acids are of two types, unsaturated and saturated. "Iodine number" (value) is the number of grammes of iodine which can be taken up by 100 grams of fat. The unsaturated fatty acids have a higher iodine number than the saturated fatty acids.

The unsaturated fatty acids are usually liquid at room temperature. They are oleic, linoleic and linolenic which are present in groundnut, soyabean and linseed oil. The commonly consumed vegetable oils are unsaturated except coconut and palm oils.

The saturated fatty acids can take up less amount of iodine or hydrogen, as palmitic, stearic and lauric, which are present in palm oil, coconut oil and tallow. The fat derived from animal origin like butter is solid at room temperature and is saturated, while fat from vegetable oils like linseed as well as marine oils like shark liver oil, is liquid at room temperature and is unsaturated.

Hydrogenation of oil is the process by which an unsaturated fatty acid is subjected to hydrogen at high temperature and converted to saturated fatty acid. By this process oil which is normally liquid at room temperature can be solidified to resemble ghee, and is marketed as *vanaspati* in India and as margarine in the Western countries.

Frisky et al<sup>14</sup> and Kinsell<sup>15</sup> administered fats of vegetable origin but of a different iodine number. By alternating the fats there was a decrease in plasma cholesterol and phospholipid level proportionate to the unsaturation of fat in the diet. Ahrens et al<sup>16,17</sup>, on giving single type of fat for periods of 5 weeks and substituting unsaturated vegetable fat for animal fats of the same caloric value, reduced blood cholesterol in normal, as well as, in persons having hypercholesterolaemia. The serum lipid level was related to the degree of saturation of fat. When

## Atherosclerosis, Role of Diet in

corn and cotton seed oils were hydrogenated and given the serum lipid level rose, compared to the same oils when given unhydrogenated. They also showed that the level of total cholesterol was 40 per cent higher when coconut oil was given (which unlike most vegetable oils is saturated) than on administration of corn oil which is highly unsaturated.

It would be therefore interesting to compare the serum lipid level on the Malabar coast of India where coconut oil is extensively consumed, with regions in the Bombay State where sweet oil is consumed. Bronte-Stewart et al<sup>18,19</sup> by feeding animal fat or hydrogenated vegetable fat found serum cholesterol level higher than when unhydrogenated vegetable fat or marine oil was used. The differentiating factor was unsaturation of fatty acids in vegetable or marine oil. Hardinge and Stare<sup>20</sup> observed that blood cholesterol level was lowest in strict vegetarians, it was higher in those who consumed more dairy products and highest in those having mixed diet.

**Essential Fatty Acids (E.F.A.):** Fatty acids which are necessary for growth are known as essential fatty acids. They are linoleic, linolenic and arachidonic, and are present in sweet oil, groundnut, cotton seed and linseed oils. Like the essential amino acids they cannot be synthesised by the body hence they have to be supplied in the diet. Linoleic acid appears to be the primary factor which must be supplied in the diet (Burr and Burr<sup>21</sup>) and it is converted to arachidonic acid in animals.

Witten and Holman<sup>22</sup> suggest that as linoleic and linolenic acids are of vegetable origin while arachidonic is of animal origin it appears that in the animal linoleic acid is converted to arachidonic acid through the mediation of pyridoxine.

Sinclair<sup>23</sup> has observed that for some obscure reason male animals require 5 times more E.F.A. than females and noted that rats kept on diet free of fats and sterol had abnormal deposit of cholesterol in the epidermis. Cholesterol is esterified with unsaturated fatty acids. When the unsaturated fatty acids are not available the cholesterol combines with saturated fatty acids and these abnormal esters are less readily disposed of and hence cause atheroma. Sinclair has also stated that 70 per cent extraction of flour tends to cause E.F.A. deficiency as during high extraction the wheat germ oil, which is an excellent source of E.F.A., is removed.

Bronte-Stewart et al<sup>18,19</sup> in South Africa on feeding volunteers with animal fats like beef dripping, butter and eggs found elevation of serum cholesterol. There was no elevation on feeding with olive oil, sunflower oil and groundnut oil. When hydrogenated groundnut oil was fed a prompt rise occurred in serum cholesterol. This could be explained that groundnut oil has predominant linoleic acid, which is an essential fatty acid but on hydrogenation much of the essential fatty acid is destroyed and unnatural trans fatty acids are formed (Sinclair<sup>23</sup>). Bronte-Stewart<sup>19</sup> therefore concluded that it was the nature of the fatty acids of the fats which determined serum cholesterol level. Keys<sup>24</sup> however does not believe that deficiency in E.F.A. exists in man. He feels that by merely reducing total intake of fat alone, serum lipid level is lowered, though total calories, proteins and vitamins in the diet are kept constant.

In the tropics the chief source of fat is vegetable oils which are rich in essential fatty acids (linoleic). Hydrogenation destroys these essential fatty acids and hence we are deprived of an important source of E.F.A. One wonders whether the present trend of eating hydrogenated oils (*vanaspathi*) therefore would increase the incidence of atherosclerosis in the tropics.

**Proteins:** Mann et al<sup>25</sup> produced atherosclerosis in monkeys by a diet of soyabean proteins and prevented it when casein was the dietary protein. This effect may be due to the slight sulphur acid content of casein. Page et al<sup>13</sup> have observed that as atherosclerosis is associated with an abundant diet it is difficult to believe that low proteins or low content of amino acids is a causative factor.

**Carbohydrates:** The exact role of carbohydrates in the production of atherosclerosis is obscure. Carbohydrates can be converted into fats as seen easily in cows which can be fattened by feeding on grass. Jefferies<sup>26</sup> showed that total blood lipids in the Chinese who consumed 90 per cent carbohydrates and proteins but only 10 per cent fats, have higher blood lipids than Americans of the same age-group, who derived 43 per cent of calories from fat. This is explained by the fact that drastic dietetic reduction of fat reduces the E.F.A. which results in high blood lipids. Therefore when reducing obese patients, when there is drastic restriction of fat, it is better to supply the quota of fat as vegetable oils so that enough E.F.A. is supplied.

**Vitamins:** Rinehart and Greenberg<sup>27</sup> had demonstrated arteriosclerotic lesions in pyridoxine-deficient monkeys. On the available evidence Shroeder<sup>28</sup> has concluded that pyridoxine with

trace metals like zinc is necessary for conversion of linoleate to arachidonate. Sinclair<sup>23</sup> has stated that only 1/3 of pyridoxine is present in a 70 per cent extraction of flour and this prevents conversion of linoleic to arachidonic acid, due to deficiency of vitamin B<sub>6</sub>.

**Summary**—1. The reduction of total calories to maintain an ideal body weight is the prime factor in prevention of atherosclerosis in an obese. is unanimously agreed.

2. It is not the quantity of cholesterol ingested but the increased intake of total fat in the diet that is responsible for the raised serum lipids.

3. Amongst fats those which have high amount of unsaturated fatty acids like marine and vegetable oils (except coconut and palm oils) lower the serum cholesterol whilst saturated fatty acids as found in all hydrogenated vegetable oils and animal fats tend to raise the serum cholesterol level.

**Conclusions**—In the present state of our knowledge the role of diet in the production of atherosclerosis is still unsettled, yet there are significant trends which can help us to guide our patients suffering from coronary disease or in those with hereditary history of cardiovascular disease.

- (a) Restrict total calories to bring down the weight to 5 per cent below the ideal body weight.
- (b) Restrict total fat to supply only 20 per cent of the total calories.
- (c) Fat intake should be made up of vegetable oils (except coconut). Hydrogenated vegetable oils (*vanaspati*) and animal fats like butter, ghee and yolk of eggs should be restricted.
- (d) Green vegetables, fruits, unrefined cereals and skimmed milk should be the main constituents of the diet.

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## Barbiturate Poisoning

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**ATRESIA, CONGENITAL, OF THE OESOPHAGUS—See OESOPHAGUS, CONGENITAL ATRESIA OF**

**BACILLARY DYSENTERY—See DYSENTERY, BACILLARY**

## BARBITURATE POISONING

*D. Bhaskara Reddy*

Barbituric acid or malonylurea though itself inert in the body, readily forms various alkyl and aromatic derivatives to produce a series of hypnotic drugs. Hence the action of the barbiturates depends upon the rate of absorption, rapidity of destruction in the tissues and on the rate of excretion from the body. Sodium salts are generally favoured. Various barbiturates are preferred in different countries. Nearly 10,000 known epileptics in the British Isles and 300,000 in the U.S.A. still use sodium phenobarbitone which is the main therapeutic agent. Misuse of barbiturates is of worldwide importance, seemingly running parallel to increasing urbanisation, increasing social achievement and standards of living. Increase in suicidal cases has been reported from various countries like Great Britain, the U.S.A., Denmark, and South Africa. 5000 to 7000 cases of acute barbiturate poisoning during the year 1956-57 in Great Britain have been recorded by Lockett<sup>4</sup>.

The clinical stages in barbiturate poisoning have been classified into 5 categories by Sunshine and Hackett<sup>5</sup>.

- |          |      |   |
|----------|------|---|
| Category | I.   | Awake, competent and mildly sedated.  |
|          | II.  | Sedated, reflexes present, prefers sleep, answers questions when roused, does not cerebrate properly. |
|          | III. | Comatose and reflexes present.  |
|          | IV.  | Comatose and a-reflexive.   |
|          | V.   | Comatose, with respiratory and circulatory difficulty.  |

The clinical condition can be correlated with reference to the blood barbiturate levels. This has been worked out in 27 patients by Sunshine and Hackett<sup>6</sup>. The patient with an initial blood barbiturate level of less than 4 mg per 100 c.cm will probably not be in a serious clinical condition unless other factors are superimposed. Any initial barbiturate levels higher than 4 mg indicate serious illness except in the case of phenobarbitone where initial blood levels higher than 6 mg per 100 c.cm are serious. Wright (1955)<sup>7</sup> has studied in 45 cases of barbiturate poisoning the relationship between blood concentration and the effect produced by the drug. Ten mg of barbitone or more per 100 c.cm of blood caused deep coma and the corresponding figure for phenobarbitone was 7 to 9 mg and for short-acting barbiturates 1 to 3 mg only. Short-acting barbiturates are particularly liable to produce shock and pulmonary oedema and they are the agents which are responsible for deaths.

Laboratory studies showed that the barbiturates are distributed throughout the body so that a fairly accurate estimate of the total dose can be made from the determination of blood level. Shortly after ingestion, a high concentration of the drug may be found in the liver but later falls to nearly that in the blood. The concentration in the cerebrospinal fluid is significantly lower. Renal clearance of barbitone is greater than that of phenobarbitone. Copeman (1954)<sup>2</sup> concluded from his analysis that liver may be used as a criterion of the amount absorbed



by the system in general, and distribution of the drug is not uniform but depends largely on the individual constitution. Veronal and luminal are considered to be less toxic judging by the amounts in the liver and kidney. The significant amount of drug may remain in the stomach unabsorbed for a considerable time.

**Treatment:** In recent times Megimide (ethyl methyl glutarimide) and amiphenazole (Dap-tazole) have been extensively used in the treatment of these cases in an attempt to bring the patient quickly out of coma. Louw and Sonne (1956)<sup>5</sup> treated 24 cases of barbiturate poisoning, 20 with megimide alone and 3 cases with amiphenazole alone and one case with both. The therapy contributed to the achievement of a state of anaesthesia without shock in 11 cases but did not reduce the period of coma in severe cases as it did not influence the rate of elimination. Complications are few and limited and when administered together are very much safer than anaesthetics previously used.

**Barbiturate Addiction:** Barbiturate addiction is a growing problem and with more people indulging in intake of barbiturates it has become a more serious problem. Its results are more harmful than those of addiction to morphine. Hunter and Greenberg (1954)<sup>3</sup> recorded 3 cases of drug addiction with barbiturates which very closely simulated spontaneous hyperinsulinism.

**Synergism Between Barbiturates and Alcohol:** There seems to be a synergism between barbiturates and alcohol. Burrows (1953)<sup>1</sup> has recorded 2 fatal cases in which death was believed to have been due to the combined action of alcohol and barbiturates. He concluded that there was an additive and possibly a potentiative action of the two drugs and drew attention to the danger of prescribing heavy barbiturate sedation for alcoholics and also advised caution in the use of alcohol in psychiatric patients under sedation with barbiturates, and emphasized once again the possibility of a barbiturate having been consumed simultaneously when dealing with a case of apparent drunkenness.

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## BARBITURATE POISONING, TREATMENT OF

V. Iswariah

Barbiturates in every sense of the word are rapidly becoming drugs of addiction leading to chronic intoxication. The acute intoxication, accidental or suicidal, with coma and possible death, needs active measures to avert a catastrophe while the addict with evidence of chronic poisoning needs primarily psychological treatment.

**Extent of Barbiturate Intoxication:** Between 1949 and 1953, about seven thousand cases of acute barbiturate poisoning were treated in different casualty hospitals of the United Kingdom (Symposium, *Lancet*, 1956, 2, 176). Mortality due to barbiturate is said to be 13 per million. Among 100,000 prescriptions analysed in the United Kingdom, no less than 9.6 per cent were for barbiturates. The annual cost to the nation of barbiturates prescribed by general practitioners in the National Health Scheme in one year (excluding hospitals) was £ 1,571,000.

The annual consumption of barbiturates in the United States of America is said to be in the neighbourhood of 300 tons (Goodman and Gillman, 1955)<sup>2</sup>. Many habituated persons continue to take 'sleeping tablets' automatically when in a drowsy state, thus adding to acute poisoning. Promiscuous sale of the barbiturate sleeping tablets over the counter, makes it one of the most "popular" suicidal agents, in the Western countries. It has also been observed that indiscriminate prescribing to weak-willed patients by 'indifferent physicians' is perhaps the single incriminating factor in acute and chronic poisoning.

Other interesting fact brought to light in the symposium referred to above was that the lethal effect of a barbiturate in many instances was due to admixture with alcohol or taking the drug when under the influence of alcohol, the two having a dangerous synergistic effect.

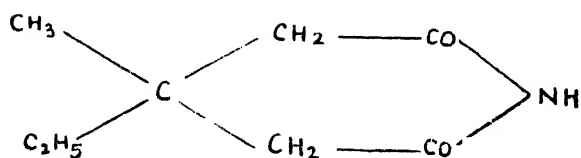


## Barbiturate Poisoning, Treatment of

**Treatment of Acute Barbiturate Poisoning :** Amiphenazole or Daptazole (DAPT) has been in use from about 1954. Shaw and Shulman<sup>13</sup> had described their action in animals under the influence of barbiturate where they shortened sleep and hastened awakening. It also held out hope of overcoming the respiratory depression of morphine ; DAPT permits morphine in large doses with safety. Shaw, F. H. and McKeogh, J.<sup>10</sup> had administered 220 mg or 3 gr of morphine to relieve severe pain of cancer. No respiratory depression, constipation, or vomiting was noticed with the combination, though the analgesic effect of the usual therapeutic doses of morphine was not much affected.

Further, it was noticed that DAPT is a general stimulant of respiration when depressed, not specifically due to morphine. Hence its mode of action differs from nalorphine. The practical utility of DAPT *vis-a-vis* morphine is in permitting the use of morphine in high doses (within limits) with safety. But the main use of DAPT is as a barbiturate antagonist.

Shaw and Shulman<sup>12</sup> had introduced with DAPT, another compound designated first NP 13 and subsequently named megimide, bemegride or glutarimide. Chemically it is methyl ethyl glutarimide with the structural formula as below.



**Possible Mode of Action:** Shulman and colleagues<sup>9</sup> claim that bemegride exerts a 'direct antagonism' to the offending barbiturate ; this is partly borne out by the resemblance in chemical structure between barbiturates and bemegride. Shaw<sup>11</sup> believes that bemegride may be a "specific antagonist" to barbiturate poisoning ; this view is supported by Holten<sup>1</sup>. On the other hand Louie and Sonne<sup>6</sup> hold that the action of bemegride is not like nalorphine *vis-a-vis* morphine, but just as a circulatory stimulant, though different from amphetamine or picrotoxin.

DAPT is said to act in a less well-defined manner, but is less toxic than bemegride, as it improves respiration and raises the blood pressure in barbiturate poisoning without causing convulsions.

**Application:** How far the simultaneous use of DAPT and bemegride is superior to either alone in the treatment of barbiturate intoxication is the subject of study in many hospitals. Available evidence seems to favour the use of the two together.

Shulman et al<sup>9</sup> were the first to use them in treating coma of barbiturate origin ; they had given 50 mg of bemegride intravenous every 5 to 10 minutes upto a total of about 1 g. When a third of this amount of DAPT was combined with bemegride, the " safe state " was restored earlier. If there was tendency to relapse, the treatment could be repeated till pharyngeal and laryngeal reflexes returned, muscle tone was restored, with improvement in the pulse, blood pressure and respiration.

Worlock<sup>15</sup>, reported successful treatment of 12 cases of acute barbiturate poisoning with the two drugs used in smaller doses. The successful treatment of a 15 months child by this method is also reported by Perinpanyagam<sup>8</sup>. But it has not been proved definitely by controlled studies if bemegride helps to destroy or excrete the offending barbiturate any quicker than simple supportive measures adopted for a comatose condition. Wright<sup>14</sup>, using ultraviolet spectrophotometric methods had shown that there is a parallelism between barbiturate level in blood and the depth of coma.

The Copenhagen workers, Pederson and Larsen<sup>7</sup>, have contributed substantially to our understanding of the mode of action of bemegride. Thirtytwo cases of poisoning with allyl barbiturate were treated by them with bemegride and compared with 74 cases not so treated. In 22 out of the 32 bemegride and amiphenazole had a definite rousing effect, but invariably the patient lapsed into unconsciousness and the treatment had to be repeated. The biggest dose of megimide alone was 3.5 g while in combination 0.7 g of megimide and 1.5 g of DAPT were used. The two drugs had not curtailed the period of unconsciousness or restored consciousness 'at higher blood levels' of barbituric acid than in the controls.

The Copenhagen workers have emphasised that these new drugs have not altered the fundamental importance of the earlier conservative and supportive treatment of coma of barbiturate poisoning. They have also pointed to the undesirable effects of bemegride itself i.e., convulsions, visual hallucination, psychosis, etc. How far are these due to bemegride itself or its working in conjunction with barbiturate is not clear.

A new method is suggested by Berman et al<sup>1</sup> based on animal experiments and human intoxication, i.e., haemodialysis with repeated spectrophotometric determination of it in plasma. Very recently, Hermun Laura and Shaw<sup>3</sup>, have reported favourably the use of bemegride in cases of acute intoxication of barbiturates complicated with alcohol.

**Chronic Barbiturate Intoxication:** Hunter and Greenberg<sup>2</sup>, based on their study of biochemical changes following chronic barbiturate poisoning, suggest that the symptoms resembled an islet-cell tumour of the pancreas. Abnormally high levels of pyruvate and glucose were observed by them in patients given glucose when intoxicated with barbiturates. But if vitamin B-complex was administered beforehand, this abnormality was not noticed.

Prolonged therapy with phenobarbitone for epilepsy in large centres has revealed high incidence of megaloblastic anaemia; phenytoin and promidone were also responsible. Folic acid helped to correct the anaemia.

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## BLASTOMYCOSIS

D. Jagannatha Reddy

Blastomycosis is mostly confined to the Americas and reports of the same from India are rare. Pinto recently recorded a case of pulmonary blastomycosis. A male patient aged 60, was seen by him for dyspnoea and cough with no fever. He observed wasting in the infraclavicular regions, fine crepitations over the bases of the lungs with slight hyper-resonance on percussion. The liver was enlarged and tender. Skiagrams of the chest showed multiple opacities and left ventricular hypertrophy. The sputum was thick and blood-tinged. No acid-fast bacilli were seen but yeast-like cells, either single or in pairs, were noticed. On maltose-agar cultures, identical organisms were recovered. Clinical improvement to stilbamide therapy was significant and this progress was marked by complete clearance of the opacities in the lungs in the skiagrams taken during treatment.

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## BLOOD GROUPS, MEDICOLEGAL ASPECTS OF

D. Bhaskara Reddy

The value of blood grouping in forensic problems is now well-established. Blood group determination is a biological test. Like all such tests it can never attain absolute reliability but it must on the whole be characterised as one of the most reliable biological tests used in forensic practice. The complete blood group determination of an individual may some day become almost as distinctive as finger prints. In some American states the law courts have the power to compel the parties to affiliation proceedings, to submit to blood grouping tests although the results are never binding on the court, whether they are obtained by compulsion or put forward voluntarily. These tests may exclude paternity but can never prove it. Unger<sup>1</sup> in 108 cases, was able to definitely exclude alleged paternity in 30 cases.

Medicolegal practice of blood grouping is limited at present to 3 systems of blood factors, namely, A-B-O, M-N and Rh-Hr systems. Each of the three blood group systems contributes to excluding paternity in a man falsely accused of being the father of a given child. The chances

## Blood Groups, Some Recent Studies in

of doing this with the A-B-O system is about 18 per cent, the M-N system about 18 per cent and the Rh- Hr system about 25 per cent; when all the three systems are used simultaneously the chance is greater than 50 per cent.

Jungworth (1955)<sup>2</sup> has described a simple technique of determining the paternity by blood group systems which depend on geno-frequency. The author claims that Kell (K) blood group system fulfils the requirements. He carried out investigations on 3000 unselected adults and it revealed that 233 were positive, the distribution being K K 0.15 per cent, Kk 7.61 per cent, kk 92.24 per cent. For forensic purposes therefore, geno-type determination is superfluous because of the great rarity of homozygotes (about 1 in 500). The use of K blood grouping is regarded as a refinement which considerably increases the possibility of exclusion especially in paternity cases in which several men are implicated.

Sometimes, group-specific investigations are also done in the identification of victims of an air disaster with the help of blood groups. Frache et al (1954)<sup>1</sup>, from the remains of the 16 victims of an air disaster near Rome, where the fragments were scattered to 200 to 300 meters radius were able to identify 11 people by serological means using (1) A-B-O (with A<sub>1</sub>, A<sub>2</sub>), (2) M-N, (3) P and (4) Rhesus group (C<sub>c</sub>, C<sub>w</sub>, D, E). With the help of other material available they were able to identify all. Race and Sanger<sup>3</sup> recently found that from 132 members of Lister Institute, London, no less than 126 could be distinguished from their colleagues by their blood group complex.

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## BLOOD GROUPS, SOME RECENT STUDIES IN

A. Sitaramamurti

In June 1953, blood specimens of an Rh-positive mother, and her Rh-positive group compatible infant, suffering from haemolytic disease, in Venezuela, were examined. Jaundice appeared in 12 hours and the infant died on the third day. In the absence of A, B, O, incompatibility the occurrence of "low incidence" blood factor with its corresponding antibody was suspected and was later confirmed when maternal serum reacted strongly with her husband's group compatible red cells, but failed to react with 200 random group O bloods (Levine et al, 1954). Levine met the father of the propositus in New York on the 26th October, 1953 and they both agreed to name the new blood factor as "Diego" (Di<sup>a</sup>). The Di<sup>a</sup> factor was not identical but different from two other low incidence blood factors Mi<sup>a</sup> and Be<sup>a</sup>. All these three low incidence blood factors are associated with haemolytic disease when tested with the red cells of the three corresponding husbands' bloods. Studies on the Diego blood factor started since then, and members of the Diego family were investigated in order to trace the genetic transmission of this new blood factor. An analysis of their data showed no apparent correlation or linkage of Diego factor with sex or any of the blood group systems studied so far. The study of this Diego factor was extended to several other populations (Miguel Layrisse and Tulio Arends, 1957) to study its distribution particularly in Mongoloid, Caucasian and Negroid populations. In Caucasian estate, negative results were observed, while in six South American Indian stocks, and two groups of Asiatic Mongoloids, it was present in high incidence. In two groups of Venezuelan Negroes also, the factor was present. The Diego antigen was found to be inherited in single dose (heterozygous) in 41 families studied, and could be followed to several generations without sex linkage. The Diego factor is suggested as part of a new blood group system, the Diego system, which could be classified as the tenth established blood system. Levine and Robinson (1957) mention that a blood of low incidence variety in one population group may have a high incidence in other population groups. Evidence is presented that the Diego antigen is independent of 15 other low incidence groups and is not genetically related to

four high incidence factors. With an increasing number of low incidence blood factors, further comprehensive studies may reveal that some of them may be genetically related as alleles or linked with other well-known blood group systems. Race and Sanger (1954) actually suggested that a low incidence factor may result from mutation in one or more of the well-established blood group systems as shown to occur for  $V^u$  and  $MNS_3$  systems and still more recently for  $Tj^a$  and  $P$  (Sanger, 1955).

Blood group substances, their chemistry and immuno-chemistry have been described by Kabet et al (1953), Kutbush et al (1955), and more recently Vaughan (1956), and their studies appear to indicate that anti-bodies to Rh, Kell, Cellano, Duffy and S antigens are typically  $\gamma$  globulin in character and that antibodies to Lewis antigen and probably to Kidd antigen are non- $\gamma$  globulin. Others, which have been reported to be non- $\gamma$  globulins are cold agglutinins and some examples of anti- $\alpha$  and anti- $\beta$ . In contrast to these findings, Hill and his co-workers (1949) suggested that non-agglutinating anti-Rh antibody was probably  $\beta$  globulin. Vaughan and his co-workers (1957) state that red cells sensitised with an anti-Rh antibody are agglutinated by anti- $\gamma$  globulin sera irrespective of the 'order' of Rh antibody activity. On the other hand, the red cells sensitised with anti-Lewis antibody are agglutinated by antisera to non- $\gamma$  globulin substances. Of the six other blood group antibodies studied, five provided  $\gamma$  globulin red cell coating materials and one an anti-Kidd a non- $\gamma$  globulin material, i.e. of the four anti-Kell (K) sera, all sensitised Kell cells with  $\gamma$  globulin and one apparently showed a non- $\gamma$  globulin component in addition. One anti-S, two anti-Cellano ( $k$ ) and two anti-Duffy ( $Fy^a$ ) sera also showed  $\gamma$  globulin sensitization characters and only one anti-Kidd ( $jk^a$ ) antibody was available which appeared to be non- $\gamma$  globulin.

Roy and Chatterjea (1957) have described the frequency of A and B blood group secretors in Bengalis. It is stated that A, B or O antigen in the saliva is inherited as a Mendelian dominant character and accordingly, the individuals generally have been divided into two groups as secretors and non-secretors, due to the fact that there are two distinctly different forms of antigens: (1) A water-soluble form absent in red cells or serum, but present in most of the organs and body fluids of a secretor (this is generally controlled by secretor gene). (2) A lipoidal form soluble in organic solvents and present in almost all tissues and red cells except in the brain and secretions (this is not influenced by the secretor gene). In a series of 7456 Bengalis (Chatterjea, 1957) consisting of 6247 Hindus and 1209 Muslims, the incidence of groups A, B, O and AB were 24.08, 36.24, 32.37 and 7.31 per cent respectively for Hindus, and 26.38, 33.25, 30.94 and 9.43 per cent respectively for Muslims. In a series of 336 Hindu males 73.21 per cent were secretors and 26.79 per cent non-secretors.

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## BLOOD STAINS, MEDICOLEGAL ASPECTS OF

*D. Bhaskara Reddy*

**Identification of Blood:** The identification of blood stains on any object in cases of homicide or accident is of great medicolegal significance. Recently Ruffie and Ducos (1956)<sup>1</sup> pointed out that precipitin and complement fixation tests for identification of human blood in stains are both too delicate and too easily subject to errors in their performance. Vacher et al (1955)<sup>2</sup> described a new and simpler test based on a modification of Coomb's antiglobulin test. Ruffie and Ducos<sup>1</sup> have devised independently a similar test using Rh positive erythrocytes coated

## Bone Marrow, Granulomatous Lesions in

with antibody from anti-D serum. The test has been applied to blood stains upto 4 years old which had been exposed to varying conditions of temperature and light on widely different materials such as canvas, wool, cotton, wood and paper. The agglutination reaction was positive with all samples of human blood but negative with blood from sheep, dog, cat and rabbit. The authors consider the test as highly specific and sensitive upto 1 in 5,000 dilutions and that in view of its simplicity and objectivity it should be used in general medicolegal practice in preference to classic methods hitherto employed.

*Age of Blood Stain:* It is equally of significance in medicolegal work to determine the age of the blood stain. Weinig (1954)<sup>3</sup> has used the migration of chlorine ions from blood stains into the surrounding material as a means of studying the age of blood stains, the method being adopted from that used to determine the age of ink writing on paper. Its application to the determination of the age of blood stains is facilitated by relative constancy of blood chloride concentration. The method is reliable except in conditions of extreme atmospheric humidity.

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## BODY FLUIDS, ROLE OF POTASSIUM IN—*See* POTASSIUM, ITS ROLE IN BODY FLUIDS AND MUSCULAR CONTRACTION

## BONE MARROW, GRANULOMATOUS LESIONS IN

R. Subramaniam

Gertrude L. Pease observed 150 cases in which bone marrow was studied by aspiration technique, from subjects suffering from tuberculosis, histoplasmosis, brucellosis, sarcoidosis, infectious mononucleosis, malignant lymphomas or miscellaneous and indeterminate disorders. Granulomatous lesion is defined as "a nodule of macrophages which have enlarged to form epithelioid cells, surrounded by a peripheral zone of lymphocytes and in some instances plasma cells, eosinophils and fibroblasts. The epithelioid cells may enlarge and coalesce to form Langhans' giant cells. However, in some cases giant cells may not be observed. The granulomatous lesion may vary in size from a single nodule to a prominent nodule, the latter occurring when neighbouring lesions coalesce. The granulomas may vary from few to many in number".

*Tuberculosis:* A diagnosis of tuberculosis was established in 11 of the 100 patients. Tubercle bacillus was identified on culture and animal inoculation of sputum or gastric washings, other body fluids or tissues. A diagnosis of tuberculous lymphadenitis was established in two patients by histological examination of lymph node. The granulomatous lesion in the bone marrow was seen in four patients having miliary tuberculosis and one patient had pulmonary tuberculosis which was identified by culture examination, etc. Acid-fast stain did not reveal the bacilli.

*Infectious Mononucleosis:* Fourteen patients were studied in this group ranging in age from 6 to 49 years. Peripheral blood smear did reveal lymphocytosis with leucocytic excess. Paul-Bunnell test was positive in all the cases. The granulomatous site in the bone marrow was identified with that described by Hovde and Sundberg. The lesions were either few or widespread and consisted of small foci of epithelioid cells or fairly prominent foci of epithelioid cells.

*Malignant Lymphoma:* Granulomatous lesions were seen in six patients with malignant lymphomas and of these five were males and one female, ranging from 7 to 56 years of age. Four of the six patients had Hodgkin's disease, confirmed by histological examination of the cervical lymph node and the remaining two, diagnosed as giant follicle lymphoma by histological examination of lymph node biopsy. The granulomatous lesions in the bone marrow showed a variable size of the epithelioid cells surrounded by few lymphocytes, plasma cells and eosinophils.

*Sarcoidosis:* A diagnosis of sarcoidosis was made in six patients—ages ranging from 30 to 64 years. Cervical node biopsy revealed non-caseating granulomatous lesions compatible

with sarcoidosis. Necropsy disclosed granulomatous lesions in the lungs. Results of bacteriologic studies were negative. Histologic examination of splenic tissues in one patient showed small discrete non-casating granulomatous lesions. X-ray examination showed diffuse nodular infiltration and bacteriological result of sputum examination was negative. Examination of the tissue from the liver and the lymph nodes in one case disclosed non-casating granulomas compatible with Boeck's sarcoid.

*Histoplasmosis:* Systemic histoplasmosis was found in four patients, three of whom were men ranging from 24 to 36 years of age. Sections of bone marrow in all the four showed numerous prominent granulomatous lesions with Langhan's giant cells, epitheloid cells, plasma cells and lymphocytes. Necrotic zones were noticed in three of the four marrows. Histoplasma capsulatum was seen on direct examination of the smear and sections of bone marrow in one case. Histoplasma capsulatum was obtained on culture of the bone marrow in one of the four cases. In one case it was recovered from the splenic tissue occurring during splenectomy.

*Brucellosis:* This was diagnosed in three cases. Blood culture was positive in a boy of 10 years of age. The bone marrow contained small granulomatous lesions composed of nests of epitheloid cells surrounded by lymphocytes and plasma cells.

*Hepatic Disease:* Evidence of hepatic disease was present in nine patients, with ages ranging from 16 to 60 years. Granulomatous lesions were found on histological examination of the tissue removed from the liver by needle biopsy. One case of splenectomy in this series of six cases, revealed granulomatous lesions in the splenectomy tissue examined histologically.

*Miscellaneous Disorders* consisted of multiple myeloma, essential thrombocytopenic purpura, congenital haemolytic anaemia, hypochromic microcytic anaemia, bilateral severe uveitis, subacute endocarditis with systemic moniliasis, acute disseminated lupus erythematosus, osteoarthritis, senile osteoporosis, Mikulicz's disease, Behcet's disease, Sjögren's disease, recurrent parotitis and erythema nodosum.

The bone marrow in 9 cases of the above group consisted of prominent foci of epitheloid cells surrounded by a few lymphocytes and plasma cells. "Granulomatous inflammatory process is notorious for its etiological diversity", according to Forbus. He listed among the causative factors bacteria, viruses, fungi, fats and oils, collagen, peculiar proteins and a variety of other organic and inorganic substances. Hodgkin's disease, rheumatic fever, non-specific granulomatosis of the intestines, sarcoidosis and mycosis fungoides were cited as illustrations of disorders, in which causative stimuli were unknown.

Unless a specific organism is identified in a granulomatous lesion there are no diagnostic features characteristic of a definite disorder. Aspiration of bone marrow is done in histoplasmosis and granulomatous lesions. These lesions were prominent and Langhans' giant cells more numerous in patients with disorders associated with granulomatous process. The increase in bone marrow was confined to patients who had histoplasmosis or tuberculosis.

Gall bladder lesions have been observed in various diseases for which no explanation is apparent. They appear to resemble the bone marrow seen in granulomatous disease although the incidence of prominent lesions with Langhans' giant cells is less. It has also been observed that the bone marrow lesions were representing part of a systemic granulomatous disorder of unknown cause. In some cases at least, the granulomatous lesions seen in the bone marrow may be a residual adenoma.

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**BRAIN TISSUE, PLASTIC EMBEDDING OF—See PLASTIC EMBEDDING OF  
BRAIN TISSUE**

#### **BRONCHIAL ASTHMA, TREATMENT OF**

*B. N. Lulla*

Acute asthma with complete remissions between attacks is usually due to foods, inhalants, or acute respiratory infections. Ordinarily, such cases are controlled by a simple specific management of the infections or of the allergic reactions. Chronic asthma on the other hand is a much more complex problem wherein other things in addition to allergy and infection often

## Bronchial Asthma, Treatment of

play more or less important roles. Obviously, some aetiological classification is necessary to serve as a guide for a rational therapeutic approach. Swineford's<sup>1</sup> classification is very useful in this respect.

*Causes of Wheezing:* Group I. Usual primary causes

*Allergy* to foods and inhalants

*Infections* of the nose, paranasal sinuses, throat and bronchi

Group II. Precipitate or intensified wheezing in asthma from other causes

*Reflex:* Nasal polyps, thyroid nodules, bronchial obstruction, nodules in the pharynx

*Physical allergy:* Drafts, temperature and weather changes

*Psychogenic:* "Life's situations"

*Non-specific irritants:* Smokes, fumes, chemicals

*Chronic lung diseases:* Emphysema, fibrosis, bronchiectasis

Group III. Asthma as a manifestation of serious disease

*Cardiac asthma:* Paroxysmal left ventricular failure

*Bronchial obstruction:* Carcinoma of the lung, benign bronchial tumours, kinks in bronchi from contracting scars, extra-bronchial compression, foreign bodies

Group IV. Idiopathic causes.

The clinical data required to classify any individual case can be obtained usually from the history and physical examination as well as, from X-ray examination and laboratory investigations and sometimes from results of skin tests. One must learn to elicit and interpret the clinical data which suggest the reflex, cardiac, psychogenic, or other types of causes of wheezing. One must also remember an old aphorism "all that wheezes is not asthma".

*Cortisone in Chronic Asthma:* A report on a controlled trial was presented by the Sub-committee on Clinical Trials on Asthma, of the Medical Research Council of Great Britain<sup>2</sup>. The effect of oral cortisone acetate was compared with that of placebo tablets in out-patient cases with chronic asthma who were also receiving routine antispasmodic treatment. The general conclusion drawn was that patients receiving cortisone had subjective and objective improvement during the first two months of treatment, to a greater extent than that in patients receiving the placebo. Early improvement with cortisone treatment was hardly sufficient to make a significant contribution to improved capacity for work, and cannot by any standard be regarded as dramatic or as great as that shown in patients with status asthmaticus. From then to the end of six months and during three months follow-up, this advantage gradually disappeared. Difficulty was encountered in withdrawing both cortisone and placebo tablets in the follow-up period. The side effects of cortisone in the doses used were not severe enough to cause any practical difficulties.

*Cortisone in Status Asthmaticus*<sup>3</sup>: The results of the trial clearly showed that in this group in which treatment with the usual antispasmodic drugs for the first 24 hours had failed to produce relief, cortisone in the dosage used was effective treatment. By the fourth day 10 of the 15 patients treated with cortisone no longer had disabling bronchial obstruction, whereas only 4 of the 17 in the control group were as well as this. At the end of the 14-day period, 11 of the 15 patients in the cortisone group but only 4 of the 17 in the control group, were free from bronchial obstruction. Two difficulties of cortisone therapy were emphasised. The danger of precipitating cardiac failure especially in patients who are known to have had it previously, and the possibility that in patients with severe bronchial infection the treatment would not be effective and could be dangerous. Another interesting feature was that in the majority of the patients, "standard" treatment was successful and after 24 hours of it, they were no longer in status asthmaticus and so were not included in the trial. It is recommended that on account of the dangers and difficulties of cortisone treatment, it should be used only after other therapeutic methods have been tried vigorously and have failed.

Thus cortisone has a place in the treatment of occasional acute seasonal episodes resistant to other forms of therapy, in patients in severe status asthmaticus and in patients developing intrinsic asthma in later life. The routine of dosage followed in the M.R.C. trials was 300 mg on the first day, 200 mg on the second, 100 mg on the succeeding four days; afterwards the maintenance dose was adjusted at an effective level. In status asthmaticus 350 mg was administered on the first day, 200 mg on the second and thereafter the dose was decreased by 25 mg a day until the withdrawal was complete.

**Chronic Asthma Treated with Hydrocortisone Aerosol:** Brockbank et al<sup>4</sup> reported that better results were obtained with an inert material than with hydrocortisone aerosol. However, there is evidence from Foulds et al<sup>5</sup> that it may be effective when inhaled as a powder.

**Broncho-dilator Therapy:** Gandevia et al<sup>6</sup> gave four commonly prescribed broncho-dilators, phenobarbitone and a placebo to fifteen patients for a week. The therapeutic effects of these drugs were assessed in terms of the patients' opinion and the forced expiratory volume at one second. The patients could distinguish the effects of the placebo, phenobarbitone and 3 of the broncho-dilators. It was concluded that though the drugs in general were producing a favourable response, only aminophylline suppositories and oral choline theophyllinate appeared reasonably reliable and effective in the dosages used. It was also concluded that the most satisfactory symptomatic treatment of wheezing dyspnoea at present available is likely to be a combination of one of the more effective broncho-dilators with small daily doses of phenobarbitone. The need for dual therapy is emphasised.

Lister<sup>7</sup> states that it is the three elements in the common syndrome of "asthma, chronic bronchitis and emphysema" namely, allergy, infection and emphysema, that require consideration. For counteracting the allergic element antihistamine and antispasmodic drugs, change of climate, restriction of tobacco, improved ventilation and improving the quality of the air reaching the lungs by improving the nasal airway and avoiding 'mouth breathing', are recommended. For infection, appropriate antibiotics and for emphysema, breathing exercises and prevention of an overexpanded faulty position of the thorax are very useful. Rest, reassurance and relaxation are also important.

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## BRONCHIECTASIS

D. Jaganatha Reddy

Surgical treatment of bronchiectasis is increasingly carried out in India. Sachdeva et al from Amritsar, review 50 cases of bronchiectasis, treated surgically by them. Forty-one out of them were male and the majority between 10 and 30 years, although some patients as young as 5 years were observed in the series. By far the largest number of cases had changes confined to the left lung and out of 293 segments involved, 234 were from the left lung of which 143 were in the left lower lobe. The authors also indicate the probable pathogenesis in their series which is as below:

Probable condition	No. of cases
Pneumonia in childhood or in adult age	22
Whooping cough and bronchopneumonia	4
Foreign body	2
Insidious onset without any obvious cause	19
Lung abscess	2
Hydatid cyst	1

Probable pathogenesis of bronchiectasis in 50 cases (Sachdeva, et al).

Sixteen pneumonectomies, 32 lobectomies and 3 resections were done and in one case the operation had to be repeated. Bronchiectasis associated with abscess of the lung was marked by adhesions. Postoperative complications of shock, haemorrhage, consolidation, hyperpyrexia, atelectasis, empyema and bronchopleural fistula, oedema of the lungs, homonymous hemianopia and management of such are described by the authors. The cases were followed up for five years and at the end of this period 40 were asymptomatic, 3 expired, 2 could not be traced and in the 5 symptoms were persistent.

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## Bronchogenic Carcinoma

### BRONCHOGENIC CARCINOMA

B. N. Lulla

**Aetiological Factors.**—Smoking and Lung Cancer: The most authoritative and painstaking study is that reported by the Statistical<sup>1</sup> Research Unit of the Medical Research Council of Great Britain. They sent out a questionnaire to over 40 thousand men and women doctors on the British Medical Register, asking about their smoking habits, and thoroughly analysed the results. The analysis showed that in this population there has been a marked and steady increase in the death rate from lung cancer as the amount smoked increased. The death rate per year rises from 0.07 per thousand in non-smokers (based upon the observation of one death only) to 0.47 per thousand in light smokers of 1 to 14 g a day, to 0.86 per thousand in "medium" smokers of 15 to 24 g a day, and finally to 1.66 per thousand in smokers of 25 g or more a day (1 g is almost equal to one cigarette). The death rate in heavy smokers is approximately 20 times the death rate in non-smokers. They also noticed that the mortality from lung cancer has been substantially and significantly greater in cigarette smokers than in pipe smokers, with smokers by both methods falling in between. Study of the deaths from cancer in sites other than the lung does not reveal, with one possible exception, any association between mortality and smoking. The exception is cancer of the upper respiratory and upper digestive tracts from which the number of deaths at present is insufficient to substantiate a possible trend.

Auerbach et al<sup>2</sup> came to similar conclusions from histological studies of post-mortem material.

Unfortunately however, the basis for considering smoking as a cause of lung cancer is exclusively statistical. If according to Hammond and Horn,<sup>3</sup> the carcinogenic effect of cigarette smoking can manifest itself in 20 months, why cannot lung cancer easily be produced experimentally?

Besides, Doll and Hill noticed that mortality from coronary thrombosis also reveals a slight but significant relationship to smoking. Three other causes of death also showed a steady increase in mortality from non-smokers to heavy smokers—chronic bronchitis, peptic ulcer and pulmonary tuberculosis. Can smoking then be regarded as an important aetiological factor in these diseases as well? In any case one is justified in concluding that smoking may cause cancer or may be harmful to health.

**Bronchogenic Carcinoma in Vineyard Workers:** Hess<sup>4</sup> observed 8 cases amongst vineyard workers using pesticides containing arsenic, for dusting and spraying. The carcinoma in these cases proved particularly malignant. The claim in favour of the occupational origin of such cancer was based on the following factors:

1. The men had used pesticides containing arsenic for several years.
2. This involved the inhalation of the carcinogenic substance in a higher dosage.
3. Chronic bronchitis and pre-cancerous lesions developed during the periods or shortly after the sprays were used.
4. The patients had external signs of chronic arsenical poisoning.
5. The latent period was sufficiently long.

**Environmental Factors:** Heuper<sup>5</sup> comments on the environmental causes—several atmospheric pollutants that may have additive, cumulative and synergistic effects. The causative agents may include fumes of nickel, chromium, arsenicals, asbestos, coal tar, vapours or mists of isopropyl oil, petroleum derivatives and radioactive ores and gases. Gasoline or diesel engine exhausts, dust of asphalted roads and carbon black of automobile tyres contain significant amounts of cancer-producing chemicals. Lung cancer death rates are significantly higher in urban industrialised areas than in rural areas. Disparity in the male-female sex ratio of lung cancer may similarly be attributed to differences in exposure to known cancer-producing atmospheric pollutants rather than fluctuations of a single factor such as cigarette smoking. Lung cancer death rates do not correlate with *per capita* consumption of cigarettes in different countries, but more closely parallel the rise in production and/or consumption of motor fuel, coal tar, petroleum products, carcinogenic metals and minerals or the construction of asphalted roads.

**Management of Lung Cancer:** Oswald<sup>6</sup> gives an excellent account of the management of carcinoma of the bronchus. He stresses that physicians have a very great responsibility in relation to early diagnosis and this becomes progressively more important as methods of treatment improve.

The most encouraging feature of treatment is the success of surgical resection in patients having well-differentiated carcinoma which has not spread outside the lungs, for in this series

there was a 50 per cent survival rate at the end of a five-year period. The results of radical radiotherapy have been disappointing—few can claim a five-year survival rate in excess of 3 per cent.

Belcher<sup>7</sup> reports on 264 patients subjected to lobectomy. The two-year survival rate was 50 per cent and the five-year survival rate 61 per cent; patients with adenocarcinoma had the best prognosis. The presence or absence of glandular involvement had a close bearing on prognosis. It is seen that the results of lobectomy in these series are as good as, if not far better, than those reported for pneumonectomy, even without considering the advantages of a lower operative mortality and a slighter loss of pulmonary function.

Levitt<sup>8</sup> assesses the uses of palliative radiotherapy. When there is threatened or actual mediastinal obstruction, persistent haemoptysis, or in certain patients if pain is a marked feature, palliative radiotherapy is usually worthwhile. Except in the presence of symptoms that demand relief, such as mediastinal obstruction, palliative radiotherapy is contra-indicated in the presence of a large pleural effusion that rapidly reaccumulates after tapping, disease that is too extensive to offer any hope of being managed with useful doses, and infection, whether septic or actively tuberculous. The best time for the administration of cortisone is three or four months after radiotherapy. The time lag is to avoid any risk of spreading the pulmonary infection that practically always accompanies carcinoma of the lung and the spread of which tends to be accelerated by radiation. Radiotherapy is of particular value in the treatment of cerebral and rib metastases.

McAlpine<sup>9</sup> has tried nitrogen mustard in 46 patients. Twenty-six patients showed some benefit for short periods. It is a useful palliative in case of a growth which has spread to the mediastinal glands or beyond, or in a case presenting symptoms urgently requiring treatment. Its main advantage is that it can be given in any hospital.

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## BRONCHOPULMONARY SEQUESTRATION, INTRALOBAR

D. Jaganatha Reddy

This condition, rather infrequently recognised by the clinician, is certain to gain more prominence with the increasing number of operations carried out on the thorax. Stephen reviews the pathology and pathogenesis of the condition and records clinicopathological findings of a case under his care.

A boy of 15 years age was admitted for recurrent bouts of fever and cough with expectoration of eight years' duration. In 1953, skiagrams of the chest showed polycystic condition of the posterior basal segment of the lung. Either bronchiectasis or lung abscess was suspected and treated with penicillin and streptomycin but with poor response. The W. B. C. count was 12,600 per c.mm with 75 per cent neutrophils. No acid-fast bacilli were detected in the sputum. Cystic disease of the right lower lobe of the lung was diagnosed on bronchographic evidence and the original diagnosis of bronchiectasis was ruled out. The right lower lobe was resected. The existence of the cyst was confirmed and an artery originating from the aorta was traced to the cyst. It was multilocular and sections did not show alveolar structure. No acid-fast bacilli were seen in the mucoid material from the cyst. Tall columnar epithelium was seen lining the cyst wall which in places was stratified. Chronic inflammatory reaction was noticed and endarteritis was also observed.

The author attributes causal significance to the aberrant artery noticed and supplying the polycystic mass. This anomalous artery was seen to course from the aorta and ascend from below the diaphragm to the pulmonary cyst.

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## Bronchus, Adenoma of

### BRONCHUS, ADENOMA OF

D. Jaganatha Reddy

Occasional reports of benign tumours of the bronchus appear in medical literature. They are disproportionately few, compared to the alarmingly high incidence of bronchogenic carcinoma. Sundaram and Betts from Vellore reviewed the literature on the subject and reported three cases of adenoma of the bronchus, while for the same period they had registered 107 cases of carcinoma of the lung. The three interesting case reports are included here.

A female aged 32, suffered from recurrent attacks of cough for five years and the real nature of the disease was missed. On the recognition of a patch of consolidation in the right lung on X-ray, tuberculosis was suspected. Bronchoscopy revealed adenoma of the right upper lobe bronchus. The lung distal to the growth was found irreparably damaged. Pneumonectomy was done and pneumonitis of the lung was seen with abscess in the upper lobe. The main stem bronchus contained a firm and nodular sessile growth and microscopic examination showed it to be cylindromatous adenoma.

A male aged 25, was treated for cough with profuse expectoration with penicillin and streptomycin. In spite of non-recognition of acid-fast bacilli in the sputum the patient was put to the discomfort of pneumothorax and pneumoperitoneum. He continued to bring out blood-streaked sputum. Clinical findings of the left side of the chest increased the suspicion of tuberculosis and bronchoscopy done on three different occasions failed to point to any growth. On the finding of total occlusion of the left main bronchus visualised through bronchography, left pneumonectomy was performed. The left lower lobe bronchus was found to contain a papillary adenoma with a small stalk. The lower lobe showed marked cystic bronchiectasis and the rest of the lung showed suppurative bronchopneumonia. The growth histologically was of carcinoid type.

A 23 years old male patient was treated for tuberculosis of the right lower lobe in spite of negative reports for tubercle bacilli. Pneumoperitoneum was induced in a sanatorium but following a lack of response bronchoscopy was carried out. A tumour 7 mm in diameter was spotted in the right lower lobe bronchus. Bronchography revealed obstruction at the level of the lower lobe bronchus. No malignant cells were seen by Papanicolaou technique. Right lower lobectomy was done and carcinoid pattern of bronchial adenoma was noticed.

The three cases cited above exemplify the clinical disguises under which adenoma of bronchus appears and patients wander from general outpatient department to sanatorium and at last land in a thoracic surgery unit for a final diagnosis of the offending nodule and for appropriate treatment.

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### BYSSINOSIS

D. Jaganatha Reddy

Cotton-mill workers, owing to inhalation of cotton dust, manifest symptoms, from mild allergy to pulmonary emphysema and right-sided heart failure, chiefly due to fibrosis of the lungs. Jackson in 1818 drew attention to the high incidence of asthma and chronic bronchitis in cardroom workers and suggested that the dust inhaled by them was responsible for the high morbidity rate. The protein moiety in the cardroom dust is capable of irritating the lung, and cutaneous tests in these patients established the allergic nature of the lesion. Poor ventilation, inadequate diet, alcoholism and variation in humidity and temperature of the cardroom predispose to byssinosis. Hollander observed in such cases at necropsy, voluminous lungs with areas of consolidation and scattered haemorrhagic spots associated with bronchial and hilar lymph nodal enlargement. Thickening of the alveolar walls with extensive areas of epithelisation was a significant finding.

Shivapuri and Maithlisaran Varma, after a brief review of literature on the subject record 21 cases of byssinosis seen by them at the State Insurance Dispensary at Patapon, Kanpur. Most of them sought medical aid for dyspnoea, asthma, or cough. They found in these patients varying grades of bronchitis, asthma or emphysema. The occurrence of pulmonary conditions stated above in factory workers, symptoms more pronounced in the evening, or symptoms usually seen on the first working day of the week—these have been the criteria employed by these authors, in making a diagnosis of byssinosis; no specific tests were carried out for confirmation.

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## CAESAREAN SECTION

K. Bhasker Rao

The incidence of caesarean section is on the increase as indications for the operation have been extended. From 1.99 per cent in 1937 it has gone up to 5 per cent in 1954 (Gordon)<sup>1</sup>. Even now, barring repeat section cases, cephalopelvic disproportion is the most frequent cause. Other indications are uterine inertia, stenosis of the lower birth canal, tumors of the uterus or old repairs of the bladder or birth tract. The number of caesareans for non-mechanical indications like antepartum haemorrhages or toxæmias is increasing. Lower segment caesarean is done in all cases except contraction ring dystocia and cancer of the cervix in pregnancy to facilitate future vaginal deliveries. Chances of subsequent delivery depend mainly on the type of previous caesarean and its indication. In 414 women operated for contracted pelvis only 27 per cent were later delivered per vaginam; whereas in placenta previa and the toxæmia group 77 per cent delivered vaginally (Cosgrove)<sup>2</sup>. In a 3 year period of study of 1027 caesareans (Connell)<sup>3</sup>, it was found that if a patient had no previous vaginal delivery, she had only 40 per cent chance of subsequent delivery per vaginam; but if she had a previous vaginal delivery followed by caesarean she had 80 per cent chance of delivery *per via naturales*. But there are certain risks involved in a vaginal delivery in previous caesareans. If the uterus should rupture, "there is no error in all obstetrics which carries a heavier penalty" (Eastman)<sup>4</sup>. With each caesarean, risk of rupture of the scar increases, though in a series of 130 cases with history of 4 or more sections, McNally and Fitzpatrick<sup>5</sup> report only 1.5 per cent of ruptures of previous scar. Large series of caesareans are now reported with very low death rate. There were 3 deaths in 2693 operations and perinatal mortality of 4.94 per cent (Gordon).

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# CALCIUM FLUORIDE AS PROPHYLACTIC IN RICKETS AND DENTAL CARIES—See RICKETS AND DENTAL CARIES, CALCIUM FLUORIDE AS PROPHYLACTIC IN

## CALORIC TESTS IN NEUROLOGICAL DIAGNOSIS

E. P. Bharucha

Hallpike and Fitzgerald (1942)<sup>\*</sup> have standardised the technique of caloric tests. Recordings of the results obtained are shown in the diagram below:

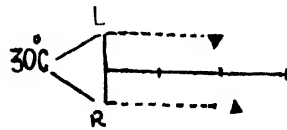


FIG 1 .

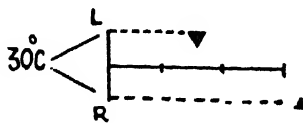


FIG 2 .

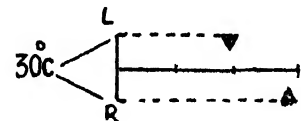
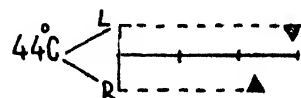
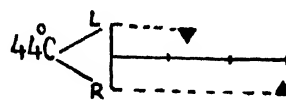
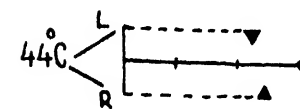


FIG 3.



Continuous line represents 3 minutes divided into 10 seconds (▲ refers to the duration of nystagmus). It is convenient to number these reactions from 1 to 4 from above downwards. Figure 1 shows a normal caloric response.

The commonest abnormality is shown in Fig. 2, a one-sided reduction of sensitivity called by Hallpike a 'canal paresis' ( $1 + 3 < 2 + 4$ ). This figure represents a left canal paresis and with a right canal paresis opposite is the case. A canal paresis suggests a disturbance in the 8th nerve (central or peripheral) or semicircular canals.

## Caloric Tests in Neurological Diagnosis

Figure 3 shows 'directional preponderance' to the left ( $2 + 3 > 1 + 4$ ) and with a right-sided preponderance, opposite is the case. Directional preponderance can occur from a lesion anywhere from the hemisphere to the labyrinth. Direction of preponderance is thought to be due to disturbance of the utricle component and canal paresis due to the disturbance of semicircular canal component of the labyrinth. Lesions of the canal or the utricle usually occur separately but occasionally they are combined i.e., there is both 'canal paresis' and a 'directional preponderance'.

Hallpike (1956) then goes on to discuss the uses of his caloric tests in the diagnosis of 4 varieties of disturbance of vestibular system:

- (1) Mènière's disease
- (2) Vestibular neuronitis
- (3) Tumours affecting the 8th Nerve
- (4) Lesions of the temporal lobe.

	<i>Aural symptoms</i>	<i>Labyrinthine</i>	<i>Audiogram</i>	<i>Caloric tests</i>
Mènière's Disease	Deafness, Tinnitus, Distortion of hearing.	Paroxysmal vertigo with vomiting.	Deafness, Loudness recruitment.	Canal paresis 49 per cent. Directional preponderance to opposite side 21 per cent. Both—in 18 per cent. Normal—in 12 per cent.
Vestibular Neuronitis	Cochlear Nil	Ditto	Normal	Directional preponderance in 8 per cent. Canal paresis in 76 per cent. Both—in 16 per cent. Normal—nil.
Acoustic Neuroma.	Perceptive deafness	Occasional vertigo.	No loudness recruitment.	In advanced cases, caloric responses absent. In early cases one or other of disturbances described above.
Temporal Lobe Lesions.	Nil or Hallucinations.	Nil	Normal	Marked directional preponderance to side of lesion.

The caloric tests are of particular value in diagnosing small acoustic neuromata, when they lie within the internal auditory meatus and have as yet produced no pressure signs.

Dusser de Barenne and De Kleyn (1923)<sup>1</sup> showed that the removal of one cerebral hemisphere in the rabbit leads to a directional preponderance of induced vestibular nystagmus to the side of the absent hemisphere. Hallpike (1956)<sup>2</sup> has shown that the particular part of the hemisphere concerned with this alteration in caloric response is strictly confined to the posterior temporal lobe.

**Conclusions:** This work of Hallpike (1956) has not only provided a means of differentiating between the various conditions producing vertigo and deafness, but it has also provided a new concept of the physiology of nystagmus. Thus no longer is one concerned with differentiating between nystagmus to the left and to the right, or reading significance into vertical and rotatory nystagmus. There are mainly 2 principal classes of nystagmus:

- (1) Those of the lower motor neurone, where the directional preponderance is to the labyrinth of the sound side, and
- (2) Supranuclear lesions, where the preponderance is towards the damaged hemisphere.

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## CANCER, ENDOMETRIAL

K. Bhasker Rao

Endometrial hyperplasia<sup>1</sup> may precede or often accompany endometrial cancer. In polyps or in hyperplastic endometrium, a carcinoma-*in situ* lesion is described, where the lining cells are large with clear eosinophilic cytoplasm and pale nuclei. According to Hertig it may take 1 to 11 years for these lesions to become invasive cancer. Squamous metaplasia may also be seen. Best results in this disease are obtained by preoperative irradiation followed by surgery<sup>2</sup>. In a series<sup>3</sup> of 531 cases, 5-year survival rate was 53.6 per cent; with intracavitary radium followed by hysterectomy it was 78.7 per cent, but with radium alone it was 49.4 per cent. By surgery alone recurrence rate at the vaginal vault is about 10-12 per cent and to reduce this incidence Kottmier<sup>4</sup> advises postoperative radium to the vaginal vault. In those cases where preoperative intracavitary radium was given no vaginal recurrence was noted<sup>5</sup>. When the growth has spread to involve the cervix, surgery should be more radical (Wertheim's) and the prognosis is almost reduced to half of what is seen in other cases where the cervix is free. In 1032 cases Kottmier reported a 5-year survival rate of 61.8 per cent and 10-year survival rate of 46.3 per cent; but when the cervix was involved, the corresponding figures were 32.9 per cent and 15.9 per cent respectively.

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## CANCER OF THE NOSE AND THROAT, IN ASSOCIATION WITH TOBACCO SMOKING AND CHEWING

C. A. Amesur

There is a widespread habit of smoking in India in the forms of bidi, cigarettes, cigars, pipe, hukka, chilim, besides tobacco chewing along with betel nuts, with or without pans. Non-smoker is a person, who has not regularly smoked one cigarette per day for 20 years, while light, moderately heavy and heavy smokers consume 1-9, 10-15 and 16-20 cigarettes per day respectively. The chain smokers smoke more than that per day.

Tobacco is irritating to the mucous membrane of the nose, throat, larynx, bronchi and through the eustachian tubes to the ear. Thus, there is loss of sense of taste and smell, besides the cough. On examination one finds multiple tumour masses covering both vocal cords.

Doll and Hill<sup>6</sup> state that the association between smoking and lower respiratory cancer is real and that the risk of dying from lung cancer increases with age and is approximately in simple arithmetical proportion to the amount smoked. Dr. Joules (London) finds in statistical demonstrations that there is increase of cancer during the current century in which smoking is also on the increase. Oberling declares that the relationship between smoking and lung cancer is that of cause and effect. Whereas Karteweg said that before long, cancer mortality will mount from 25 per cent to 40 per cent in lung cases and that this increase is *pari passu* with increase in sale of cigarettes. Hilleboe agrees with these views.

Amesur (1955)<sup>1</sup> emphasised the fact that cancer of the throat is on the increase and more so in those sections of our people who are smoking or chewing tobacco. The Maharashtrian women who frequently chew tobacco get cancer of cheek.

Graham Wynder and Croninger proved the presence of carcinogen in cigarette smoke by producing cancer in 44 per cent of the mice, whose skins were painted with mild solutions of the cigarette smoke. No cancer was found in the control series. The United Kingdom experiments made by painting with nicotine could not produce cancer in mice in 18 months. This suggests that cigarette paper is an additional factor in causing cancer in the U. S. A., reports. Rafoo from a study of 79,000 patients concluded that tobacco smoke contains benzpyrene which is carcinogenic. Hammond says that among the smokers of pipes, cigars or both, the death rate from all forms of cancer is 32 per cent above in non-smokers, whereas among heavy cigarette smokers, it is 156 per cent higher than non-smokers. The cigarette smoker runs the risk of the cancer of lung, pipe smokers of the lips and cigar smokers of the tongue. Hot smoke from the cigarette holders and pipes causes irritation and in time, cancer of the lip, tongue, mouth or larynx. Minnessti experiments show that chewing tobacco causes leukoplakia and then cancer.

## Cancer, Views on the Control of

Hilding's<sup>5</sup> experiments resulted in the following conclusions :

(a) The mucus blanket in the tracheobronchial tree, when made observable by India ink, may be made to impinge upon and accumulate at an artificially de-ciliated island as upon an obstruction. It may remain for a matter of hours upon such a spot while ciliary action and streaming of mucus continues in surrounding areas.

(b) Accumulations of cigarette tar may be similarly produced by smoking 10 to 20 cigarettes into the trachea at a comparatively low pressure.

(c) If the slowing or interruption of normal ciliary streaming at nonciliated islands in the tracheobronchial trees of smokers is at all comparable to that occurring at the artificially de-ciliated islands then the resulting accumulations of concentrated tar at isolated spots would duplicate closely the conditions of the experiments of carcinogenesis on the skin by means of tar. There lies the crux of the matter—are there such accumulations on naturally occurring squamous islands? From other data, this would seem to be probable. These experiments, taken alone are suggestive but do not demonstrate it.

(d) This process of piling up of noxious material upon nonciliated islands by ciliary action during normal ciliary drainage, rather than a deposit during inspiration either from direct impact or because of eddies in air flow, could be the key to carcinogenesis in the bronchial tree from any inhaled carcinogenic substance of whatever nature.

Possibilities are suggested for the relation of ciliary streaming to carcinogenesis involving the cords and to post-operative implantation in the trachea.

Experiments by the American Medical Association show that filters made from cotton crepe paper-fibre, sulphaflex, activated charcoal, micronite, are a mere illusion and not safe. The term denicotinized is a misnomer, for the cigarettes are not nicotine-free.

Sanghvi, Rao and Khanolkar<sup>8</sup> from Bombay report that the effects of smoking and chewing tobacco in relation to cancer under Indian conditions are : (i) chewing tobacco is associated with cancer of the oral cavities and (ii) that the combined habit of smoking and chewing is associated with cancer of the oropharynx and oesophagus.

The common Indian form of smoking is known as 'bidi' in Western India and 'biri' in Northern India. In this, tobacco flakes are rolled in dried leaf. Biri resembles in its effects European cigars rather than cigarettes. Sarma finds cancer of the larynx in Assam in 51 per cent of the cases (1951); the figure has gone up in recent years, whereas the figures from Bombay as reported by Khanolkar are 12.5 per cent.

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## CANCER, VIEWS ON THE CONTROL OF

D. J. Jussawalla

For a proper understanding of the modern concepts of cancer control, one should view the problem from two angles : (a) relative to prevention, and (b) relative to cure.

**Cancer Prevention.**—One can best treat this aspect of the subject by considering :

(1) local measures concerning identification and excision of tissues showing various pre-cancerous changes,

(2) general measures concerning :

(a) external causes aimed at the identification and removal from the physical environments, of all factors likely to produce cancer,

- (b) internal causes aimed at the identification and correction of abnormal body chemistry which may ultimately lead to cancer at a later date ; also taking into account methods that are likely to increase the internal resistance of the body to cancer.

**Cancer Cure.**—The main goal here is to destroy all cancer cells that may be present in the body.

- (1) Whilst still localised to the organ of origin or to immediately adjacent tissues, by :
  - (a) early diagnosis when it is so localised, or
  - (b) by utilizing improved methods of removal by surgery or radiation, of the deposits of cancer wherever identified.
- (2) after dissemination to distant parts of the body :
  - (a) by means of agents destructive to cancer, and
  - (b) by means of agents which can change the chemical environments of the body thereby making it difficult for cancer cells to flourish.

**Cancer Prevention.**—1. *Local Measures:* Removal of leukoplakia and associated conditions, excision of certain types of moles and warts and correction of vitamin deficiencies, take pride of place. Much work is going on in analyzing body structures of different types with a view to finding out the preponderance of specific kinds of cancers in certain organs according to the bodily habitus of the individual. On the basis of these statistical findings a careful watch can be kept on people of different body types, directed to the particular areas implicated.

2. *General Measures:* External causes. Many causes of cancer are well-known but are frequently forgotten. Pride of place goes to environmental causes of cancer, as for example, watch-dial painters ingesting radium by licking their paint brushes and developing bone cancer and leukaemia ; X-rays and radium causing leukaemia and skin cancer ; certain agents met with in chrome-manufacturing industry causing lung cancer ;  $\beta$ -naphthalene and benzidine (dye industries) causing cancer of the urinary bladder ; unknown agents in nickel-refining and isopropyl alcohol manufacture giving rise to cancer of the nasal sinuses, and finally radioactive fall-outs from atomic explosions containing strontium, which lead to bone sarcoma and leukaemia. Practical safety measures can be adopted when the number of individuals involved in this exposure is small and the exposure is unusual.

However, we are now being faced with problems, in which it is more difficult to identify and eliminate factors to which a broad segment of the population is exposed. Moreover, these factors are more or less imperceptible and form a part of our daily routine. We face such a task in the association between lung cancer and cigarette smoking. A rare disease amongst Western nations only 20 years ago, lung cancer is taking a frightful toll of lives to-day. A number of controversies have naturally developed even amongst doctors and research workers, but the general consensus of opinion is that the risk of developing lung cancer increases in direct proportion to the duration of smoking and the amount of cigarette smoke inhaled. The first problem is therefore to develop a safe filter that would remove most of the tarry residue found in smoke. Filters can be made to-day that would remove forty per cent of the tar from the smoke. This type of filter has still not been put on the market, but when it becomes commercially available, a significant reduction in the occurrence of lung cancer can be predicted.

A most interesting finding has been the association of temperature at which tobacco is burnt, with the ability of the smoke filtrate to cause cancer in the experimental animal. Present day cigarettes burn at 880° C. It is possible by adding chemicals or by changing the cut of the tobacco to ensure that this burning temperature is reduced. Experimental evidence available to-day seems to indicate that if the tobacco can be made to burn at temperatures around 600° C. no cancer-causing substances will be present in the smoke. The second interesting finding is, that most of the cancer-causing agents present in the tobacco leaf are contained in the waxy outer coating. When this dangerous layer is removed by solvents the cancer-causing factors seem to be eliminated. The third promising finding is the isolation of an important fraction of the total amount of tar which appears to contain most of the cancer-causing activity. This represents a mere 1.5 per cent of the total tar and is made up of several chemical components. Further identification and elimination by various chemical procedures or differential filtration should prove very promising.



## **Cancer, Views on the Control of**

Smoking also seems to play an important part in the causation of cancer in various parts of the mouth and throat. It is very intriguing to note that these factors somehow seem to differ from those already established from lung cancer. Whereas cigarette smoking is more liable to produce lung cancer, cigar and pipe smoking seem to be indicted in mouth and throat cancer. Excessive consumption of alcohol seems to contribute to the development of cancer in these regions, but does not seem to have any relationship with the production of lung cancer. There is a definite association between the environment and development of cancer in various parts of the body. The final answer has not yet been found but studies are proceeding apace in different parts of the world.

**Internal causes :** Most cases of cancer do not seem to have any external cause responsible for their development, and workers are convinced that the participation of an internal factor in the body itself is necessary for the production of the disease. There is a lot of evidence to-day that implicates the endocrine system in this charge sheet. An imbalance of various internal secretions is under strong suspicion, and it is believed that production of hormone abnormality either in quality or quantity may cause cancer and a number of other disorders. The main glands implicated are the sex glands, the adrenals, the thyroid and the pituitary. It is thought that a flaw or inherent defect in the genes may be responsible for this abnormality which leads to faulty hormone production. Details of this qualitative change are being pursued with great enthusiasm by some of the leading research centres of the world. Most of the hormones formed by the adrenal and the testes have been identified and their normal break-down products defined. Similar studies are proceeding in connection with the ovaries. With greater knowledge of the subject it becomes evident that this complex field of study will eventually lead to great discoveries. It is apparent that hormones exist in the body, with undreamt of activity and great potency, and perhaps defects in the production of these hormones may eventually give us the answer to our problem. Hormonal influences are being studied on various blood compounds, and an association has been found between lipo-proteins and various types of breast diseases including cancer, in women. This carcinogenesis must be under the influence of a wide variety of external, hormonal and genetic factors in the environment of the cell, that is to say, the endocrine status and constitution of the host. The study of carcinogenesis still remains the central approach to cancer research.

It can thus be seen that the process of carcinogenesis can be incited by a wide and heterogeneous range of chemical and physical agents, hormonal imbalance, dietary modifications, endocrine status and constitution of the host.

**Methods to Increase Internal Resistance to Cancer.**—When any foreign tissue, bacteria or virus enter the living body, it resists the onslaught by forming substances called antibodies, which are essentially protein molecules shaped in such a way as to fasten themselves on to a particular invader called the antigen. Antibodies are thus the means by which our body fights off infection. Active immunity exists when specific antibodies against a particular disease are present in the blood. These antibodies can be produced by injecting killed or slightly altered versions of the disease-causing organism. This principle is now being attempted against some types of cancer. Besides this, immunology also plays a major role in disease detection. For example, the W.R. test for syphilis, one of the most specific diagnostic tests we know of, is based on the detection in the blood of the specific antibody against the spirochaete of syphilis. Already the use of antibodies have been found to aid in the diagnosis of one rare type of cancer, at the Sloan-Kettering Institute in New York.

**Virus Studies.**—One aspect of virus studies concerns the role of viruses as a cause of cancer and their use to produce a vaccine for cancer prevention. There have been sporadic attempts to generalise and prove that all cancers are virus-inspired but there has been no evidence so far to show that viruses play any important role in the development of “human” cancer. There is however a distinct possibility that with the development of an effective vaccine against mammalian cancer, it may one day be possible to prepare a vaccine against other types of animal cancers also, including some forms of human cancer.

A very important advance in our knowledge of viruses has come with the finding that they are made of nucleic acids encapsulated in protein. Antibodies are known to form only against the protein portion.

Sloan-Kettering investigators have succeeded in demonstrating the presence of viruses in two types of cancer in animals. When tissue sections of cancer were examined under the microscope,

antibodies could not be found in cancer cells which were dividing rapidly but were only found in a small proportion of cancer cells which were not proliferating fast. It seems that cancer-causing viruses exist probably in two stages : as an antibody evoking complete virus (composed of nucleic acid plus protein), and secondly as an incomplete virus, a pure nucleic acid concealed within the cell. A complete virus is the form in which it is passed from one host to another. This brings together two main schools of thought on the causation of cancer, the one believing that cancer is caused by an invading external agent, and the other holding that cancer represents a mutation which involves a change in the nucleic acid of the cell. If a virus functions as a pure intracellular nucleic acid, the dividing line is extremely fine indeed.

Disoxyribonucleic acid is the unique chemical found in the nucleus of a cell. It is known to transmit hereditary characteristics. There is strong evidence that an alteration in DNA may cause a cancer cell to be produced, and that a faulty DNA is transmitted from the parent cancer cell to the daughter cancer cell.

**Cure of Cancer.**—Localised Cancer; Early Diagnosis. To-day a cure for cancer hinges on early and accurate diagnosis, though it is true that the pathological character of the cancer cell in many instances decides the fate of the host, irrespective of early diagnosis. Almost one-half of all cases of cancer can be cured if we can detect the disease early. Perhaps a diagnostic blood test, perhaps an immunological Wasserman-like reaction or perhaps better screening techniques will bring that day nearer.

**Role of Enzymes:** As enzymes are known to-day to be involved in every single chemical function of the body, they have been studied in great detail. A specific enzyme exists only for one chemical task. In certain conditions of damage to a body cell a specific enzyme may be released in the blood stream and forms the basis of this kind of research. At the Sloan-Kettering Institute the enzyme GO-T (glutamic oxalacetic transaminase) was studied because it was believed to be involved in cancer growth. This enzyme is found in maximum concentrations in the heart and liver tissues and its blood level seems to get elevated whenever these organs are impaired by disease, e. g. in coronary thrombosis, hepatitis or cancer. Enzyme diagnosis is a new concept of great promise. GO-T measurements have been shown to reveal latent liver cancer and in a proportion of patients this is the only known factor that can give an indication that cancer has spread to this organ. Such knowledge is naturally of great importance in patients being considered for major surgery. It was further found by the Sloan-Kettering team that the enzyme L-D (lactic dehydrogenase) was present in much greater amounts in fluids surrounding cancer cells, probably as a by-product of cancerous growth. Thus the presence of this enzyme in spinal fluid or pleural effusion may similarly be proved to be caused either by cancer. L-D was again found to be increased in mouse blood, before a virus-induced leukaemia could present any signs. Possibly the cells that are changing to cancer show an abnormal chemical behaviour and exhibit a different pattern of enzyme production before cancer finally becomes manifest. This work is now being applied to the study of human cancer by the New York group and is being followed with great interest throughout the world.

**Improvements in Supportive Surgical Techniques:** Surgery yet remains the most effective method available for cancer control today. For example, the use of the artificial kidney has found a distinct place in the post-operative treatment of cancer patients during acute kidney failure following radical surgery for cancer.

Injection of cytotoxic drugs like the various mustards at the time of surgery and immediately following, seems to show promising results, though complications do occur. A total dose of 0.4 mg/kg body weight appears adequate for this purpose.

The administration of male hormones after major surgery for stomach cancer has been found to be very beneficial in restoring nutritional deficiencies that occur as a result of this operation. Cortisone products to combat surgical shock, and extensive use of the electro-cutting cautery have proved of great help in increasing the scope of surgery.

**Improvement of Radiation Techniques:** A new method to measure precisely the radiation dose in phantoms corresponding to human tissues, was reported at the Atoms for Peace Conference held recently in Geneva. A phantom man has been produced containing a complete human skeleton and other special tissues like bone marrow and lungs, to directly measure the amount of radiation received by different organs. This seems to be an exceedingly sensitive technique to define the exact amount of radiation received by the bone marrow from various forms of radiation.

## Cancer, Views on the Control of

It is of great significance because of the new theory that small amounts of radiation repeated frequently, may cause leukaemia or bone cancer.

The use of ultra-high energy radiation has improved the end-results of treatment of deep-seated cancer. Moving-beam Tele-Cobalt machines and Betatrons are being increasingly utilized to combat certain types of cancer, because the skin and bones are spared the danger of necrosis that they are liable to from routine deep therapy, whenever the dosage range has to be pushed, to build up an adequate cancericidal dose for tumours away from the body surface.

**Improved Surgical Techniques:** A word must be mentioned here about the modern development of hormone surgery. In advanced cases of cancer which are hormone-dependent, such as the breast, prostate, ovaries, etc., hormone reversal by the removal of various internal secretory glands produces remissions for varying periods in a large percentage of cases. Special mention must be made of bilateral adrenalectomy and pituitary ablation, either by surgery or radiation. The adrenals can be removed with impunity along with the ovaries or testes as the case may be, for advanced cancers of the breast or prostate, provided adequate substitution therapy is undertaken. Pituitary ablation however, does not necessitate continued presentation of cortisone compounds every time, and for this reason it might be the treatment of choice in patients in lower income groups, even though the over-all mortality is much higher for this operation.

**After Dissemination to Distant Parts of the Body :** By means of agents destructive to cancer: Every year over 50,000 synthetic chemicals, antibiotic cultures, hormones and botanical extracts are being tested in various laboratories throughout the world for anti-cancer activity. These various preparations can be broadly divided into 4 categories as follows:

(i) Polyfunctional alkylating agents which are mainly cytotoxic drugs that affect both normal and malignant cells. They introduce alkyl groups into molecules, in the place of hydrogen. They are sometimes called radio-mimetic, because the cellular damage they inflict resembles that caused by radiation. The commonly used ones are, nitrogen mustards, including sulphur and aliphatic mustards; ethylene-amines including TEM, TEPA and ThioTEPA; sulphonic acid esters including myleran, chlorambucil, nitrovin, colcemid, degranol, etc. Their exact mechanism of action is not quite clear but these drugs seem to have selective toxicity for rapidly proliferating cells. More recently, chloroquine mustard is being tried out and is supposed to have a more selective action. They cause chromosomal abnormalities, induce mutations, and inhibit the growth of transplanted animal tumours in the laboratory.

(ii) A group of antimetabolite agents which compete with essential metabolites. These were first tried out in the year 1948 when folic acid antagonists were utilized for treating leukaemia. A later product of research has seen the emergence of purine and pyrimidine derivatives, which are antagonists of both folic acid and purine. They prevent the use of single carbon atoms by the cell, in the synthesis of amino-acids, purines and pyrimidines.

The importance of nucleic acids in the growth of cells makes the synthesis of these compounds the logical point at which to attack the cancer cell. Unfortunately so far, the anti-cancer activity is not fully selective, and these drugs also affect normal cells. The most efficient folic acid antagonists are the 4-amino derivatives of folic acid, aminopterin and amethopterin. They prevent the conversion of folic acid to the citrovorum factor, which is so essential in maintaining cellular metabolism. These drugs somehow "fool" a cell into accepting them as food, and then proceed to create a metabolic block within the cell, in the pathway of purine and pyrimidine. They are mainly used orally, in the treatment of lymphoblastic acute leukaemia. Remissions up to six months and more are known to occur in over 50 per cent of patients. However, with continued treatment the disease becomes resistant to these drugs, and other forms of therapy are required. Toxic manifestations have to be guarded against.

The purine antagonist 6-mercaptopurine is useful in acute leukaemia of children. Chronic leukaemia, Hodgkin's disease, multiple myeloma and other malignancies do not seem to be affected by this drug. 6-thiopurine and 6-chloropurine are analogous to it. Other essential metabolic processes can be blocked by similar but different antagonist substitutes. Thus, for example, amino acid analogues have been prepared which compete with the up-take of essential amino acids in the tumour. The ethyl analogue of methionine, "d,l-ethionine" is one such substance. Some of these compounds may also prevent the utilization of serine and methionine, thereby blocking nucleic acid synthesis. Combination therapy of such antagonists may be of value in overcoming cell resistance.

(iii) Antibiotics. Large numbers of compounds have been isolated from antibiotic culture filtrates, which are by-products of the industrial search for better antibiotics. Some of the most promising are Azaserine, DON, Actinomycin C and D, Puromycin, Amicetin and Sarkomycin.

Azaserine, which interferes with purine synthesis, has proved very valuable in the treatment of acute leukaemias in children, in combination with 6-mercaptopurine. DON has a similar structure and also interferes with the synthesis of purines. Actinomycin C is occasionally useful in Hodgkin's disease, and Actinomycin D in Wilm's tumour in children. The other drugs are useful only in the treatment of cancer in the laboratory animals.

There is also a miscellaneous group of drugs known to have cancericidal effects. Thus, urethane and potassium arsenite are useful in treating chronic leukaemia, and urethane also has an important part to play in controlling multiple myeloma for long periods.

(iv) Radioactive isotopes. It may suffice for the purpose of this article to mention that the use of radioactive isotopes is one way in which the cancer cell can be attacked from within the body. Large sources may be used externally as a substitute for deep X-ray therapy, as for example the Cobalt bomb, but an important use of these agents is also to attack the cancer cell from within when directly injected in a body cavity such as pleural or peritoneal spaces or when implanted in a tumor in the form of pellets, threads, needles, liquid, etc. A few of these radio-isotopes may be given by mouth and made to concentrate in different tissues e. g. iodine in thyroid, zinc in the prostate, etc.

*Viruses:* Development of anti-cancer viruses has opened a new vista in cancer research. Viruses are minute particulate sub-microscopic units, incapable of independent reproduction. They reproduce only by clamping on to living cells and acting as parasites. In doing so, these viruses divert to themselves essential chemicals of the victimised cell. This frequently results in the death of the host cell. They are capable of injuring one kind of body cell, leaving the others unharmed, doing exactly what we try to do artificially with chemicals. Several viruses have been found that adversely affect human cancer, either in the test tube or when growing in a laboratory animal. To-date however, this form of study has not proved fruitful in terms of practical results. Fluorescent antibody techniques have demonstrated that one type of virus not only localizes but is actually found within the cell, but somehow this virus seems to lie dormant, and ways and means are being tried out to activate this saboteur within the body of the cancer cell.

*Destruction of cancer cells after dissemination to distant parts of the body, by means of agents which can change the chemical environment, thereby making it difficult for cancer cells to flourish:*

Here we have to consider creating a change of the hormonal balance in the body. One can produce this by way of surgery as mentioned above, or by radiation or artificial presentation of hormones to the body. An interesting technique that may be mentioned is the implantation of yttrium 90 in the pituitary for the control of advanced cancers which are hormone-dependent. An interesting sidelight of research to change the environment of the cancer cell is the work now being done to study the effects of certain metals on the human organism as a whole. It is thought that they may have an important part to play in diseased states including cancer.

**CANCER OF THE CERVIX—See CERVIX, CANCER OF**

**CANCER OF LARYNX AND ADJACENT PARTS—See LARYNX AND ADJACENT PARTS, CANCER OF**

**CARBON DIOXIDE THERAPY IN PSYCHONEUROSES—See PSYCHONEUROSES, CARBON DIOXIDE THERAPY IN**

**CARBON MONOXIDE POISONING**

*D. Bhaskara Reddy*

Statistics show that though suicide by domestic coal gas has increased steadily, accidental death from the gas has multiplied to even more alarming degree. 400 to 500 cases of accidental poisoning from domestic coal gas in England and Wales occur every year. Simpson (1954)<sup>1</sup> reported a series of 100 cases of accidental poisoning which occurred mostly in people over 60 years. Increasing age brings forgetfulness and infirmity which together with defective hearing

## Carcinoma, Primary, of the Middle Ear and Mastoid

and sense of smell, increase the risk of accidental exposure. Many elderly persons live alone and the incidence is at its highest among them. Henderson<sup>3</sup> estimates that death will occur if an atmosphere containing 20 parts per 10,000 of carbon monoxide is breathed for 4 hours or 40 parts per 10,000 per hour. Simpson<sup>2</sup> is of the opinion that fatal saturation in the elderly or unfit may be as low as 30 per cent.

Simpson (1955)<sup>2</sup> emphasizes the ease with which deaths can occur from accidental carbon monoxide poisoning and may be overlooked in spite of the exercise of reasonable vigilance. In a series of 100 cases of accidental poisoning no fewer than 46 were unrecognised until post-mortem examination. He also pointed out the three most important medicolegal aspects of carbon monoxide poisoning, the first being the difficulty of low saturation of carbon monoxide in blood, especially of the elderly, the drunk, and those who are ill, secondly the danger, by misinterpretation of symptoms, of raising suspicion of crime where none in fact exists and thirdly the rate of post-mortem disassociation of CO-Hb which is much slower than has been assumed in the past. Old people usually die as a result of carbon monoxide poisoning. In 100 cases recorded by Simpson, 49 were 70 years old, 11 were suffering from active disease, and 7 were drunk. The CO-Hb saturation varied from 23-52 per cent. Great technical care is not necessary to obtain reliable blood specimens and that a delay even of several days causes very little significant fall in CO-Hb saturation value.

Hartridge<sup>4</sup> reversion spectroscope renders the spectroscopic detection of CO much more delicate and also allows of a rapid approximate quantitative determination.

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## CARCINOMA BRONCHOGENIC—See BRONCHOGENIC CARCINOMA

### CARCINOMA, PRIMARY, OF THE MIDDLE EAR AND MASTOID

J. V. DeSa

In a series of 29,727 cases of malignant diseases encountered between the years 1936-50, in the United Birmingham Hospitals, 19 cases of carcinoma of the middle ear and mastoid have been reported. The incidence was 0.06 per cent.

Early diagnosis is of utmost importance. Any case of chronic otitis media in which the discharge suddenly becomes profuse or blood-stained should be regarded with suspicion. Pain supervening on a chronically discharging ear is of serious significance.

Discharge from the ear, pain, deafness, giddiness and tinnitus are the most frequent symptoms whereas bleeding from the meatus, flagrant granulation tissue, bleeding polyp, facial paralysis and enlarged lymph nodes in the neck form the important signs.

Real difficulty is experienced in distinguishing between simple granulation tissue and early malignancy on clinical grounds. Cytological examination of the ear discharge using Papanicolaou technique and a timely biopsy will save many misfortunes.

**Treatment :** The treatment is either radiation or surgical excision. The best results so far have been claimed with combined therapy—surgical excision followed by deep X-rays to the whole of the temporal bone including the area of the operation. No surgical procedure can be called over-radical in this condition, since Brown advocates that in every case of epidermoid carcinoma of the temporal bone complete excision of the temporal bone should be done and followed by deep X-ray therapy. The results with radium beam were better than 200 K. V. X-ray therapy. It is expected that more satisfactory results will be achieved with newer high voltage machines. However, good results can be anticipated only if the treatment is undertaken when the disease is early.

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## CARDIAC ARRHYTHMIA

*Arrhythmia in Myxoedema* : Bradycardia is the usual rule in myxoedema. Talwalkar<sup>1</sup> has reported an interesting case of myxoedematous patient who had a sinus rate of 150 per minute associated with A-V block of changing type. The ventricular rate varied from 65-90 per minute. The patient had also attacks of paroxysmal auricular fibrillation. A normal sinus rhythm was restored to by thyroid administration.

*WPW Syndrome* : The mechanism of WPW syndrome is ill-understood. Various theories have been put forward to explain the nature of this irregularity. Out of many hypotheses of different concepts, two are compatible with the cardiac physiology. One puts forward the theory of an hyperexcitable ventricular focus responding prematurely to certain stimuli (mechanical or electrical), influencing atrial activity and occasionally leading to an outburst of rapid heart action. The other concept implies the presence of one or more accessory conduction pathways bypassing the physiologic impulse of conduction to the A-V node. To study which of the above concepts is more properly applicable to explain the WPW syndrome, 5 selected case studies were undertaken by Pick and Katz.<sup>2</sup> They have reported in details the cases with E.C.G. findings. They concluded that one or more anomalous A-V connection could most appropriately account for all aspects of the WPW syndrome. That is the second hypothesis which explains all the facets of the syndrome.

*Digitalis and Cardiac Arrhythmia* : It is well known that arrhythmia due to digitalis is common because of the narrow safety margin of the drug and the lack of appreciation of early signs of toxicity. In a symposium<sup>3</sup> on digitalis intoxication, certain facts have emerged for consideration while digitalis is being used for therapy in congestive failure. The increasing use of glycosides with latent period of action, is an important factor in the production of arrhythmia. Auricular fibrillation may itself be a sign of digitalis toxicity in a person. Hypopotassaemia may occur and thus precipitate other irregularities.

*Digitalis and Arrhythmia in Relation to Carbohydrate Metabolism* : One of the dangers of digitalis toxicity is precipitation of ventricular arrhythmia. A relation between digitalis toxicity on the one hand and the potassium metabolism and the effect of administration of potassium salts once arrhythmia has set in or as a preventive on the other, has been established<sup>3</sup>. Changes resembling potassium deficiency in carbohydrate-induced hypopotassaemia suggest a relation between carbohydrate metabolism and digitalis intoxication. Page<sup>4</sup> has reported 7 cases of precipitation of ventricular arrhythmia because of simultaneous administration of glucose and a glycoside of digitalis. Ventricular arrhythmia was precipitated on 10 occasions after administration of 100 g of glucose by mouth, on 3 occasions after a heavy carbohydrate meal and once each after 50 c.cm of 50 per cent and 10 per cent glucose were administered intravenously. It is explained that the fall in the plasma potassium was due to the entry of the potassium in the hepatic cells during deposition of glycogen. An alternative has been suggested according to which the fall in the plasma potassium is due to extracellular alkalosis of the postprandial alkaline tide.

*Treatment* : Ventricular arrhythmia precipitated by administration of digitalis is best treated with Pronestyl. The route of administration as found safe<sup>3</sup> is the oral and the dose recommended is 0.5 g four times a day. A new drug, Ambonestyl (2-diethyl aminoethyl-isonicotinamide), having the same potential action as procaine amide or quinidine, has been tried as a ventricular anti-arrhythmic drug by Clark and Esten<sup>5</sup>. The drug has the advantage of having a less potent action on the conducting system and also being less hypotensive in its action. The authors have observed the drug to be of special value in controlling cardiac irregularities during anaesthesia and cardiac surgery.

Nardostachys jatamansi, an indigenous Indian drug has been tried as an antifibrillatory measure by Arora and Madan<sup>6</sup> experimentally on dogs, and clinically on human beings by Vakil and Dalal<sup>7</sup>. In experimental acetyl choline-induced fibrillation, the drug brings about a significant reduction in the duration of auricular fibrillation. Clinically the drug did not influence the number of ectopic beats with a moderate dose, but massive doses reduced the number of auricular as well as A-V nodal extrasystoles. In auricular fibrillation the drug had no effect.

## Cardiac Failure, Congestive

Antiarrhythmic action of chlorpromazine hydrochloride has been investigated and compared with quinidine in experimentally produced auricular fibrillation by Arora and Madan<sup>8</sup>. They found that chlorpromazine administered intravenously brought about a significant reduction in the rate of auricular fibrillation and effectively prevented the occurrence of ventricular arrhythmia but unlike quinidine failed to reach the end point.

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## CARDIAC FAILURE, CONGESTIVE

L. K. Ganguli

**Aetiology.**—Deformity of the chest is often overlooked as the primary cause of congestive heart failure. That it is an important aetiological factor has been stressed by Fisher and Dolehide<sup>1</sup>. They have pointed out that gallop rhythm and murmurs simulating rheumatic heart disease commonly lead to misdiagnosis.

Blood volume measurements with radio-isotopes ( $P^{32}$ ) in patients with cardiac decompensation due to vascular or valvular disease was a subject of study by Nylin<sup>2</sup>. He has shown that the red cell volume is increased during decompensation. Gunton and Paul<sup>3</sup> in a similar study have reported that the blood volume is greater than normal in congestive failure, and that it is due to an excess of both the red cells and the plasma. With compensation the decrease in the plasma fraction is much more rapid than the red cell volume.

**Venous Tone :** Increasing attention is being paid to the role played by peripheral venous tone in producing cardiac decompensation. Wood et al<sup>4</sup> have studied the venous tone in patients with congestive cardiac failure with a comparable control group. They could not find any correlation between the degree of venous constriction and the magnitude of venous pressure elevation. The venoconstriction tended to decrease as the patient improved on a successful therapy.

**Treatment.**—Ligation of the vena cava: The effects of inferior vena cava ligation in mitral valve disease, either alone or combined with aortic lesion as reported by Bernath et al<sup>5</sup>, are encouraging. They found immediate postoperative improvement in dyspnoea. Hepatomegaly and oedema disappeared later. The death rate was 13 per cent and the common cause of it was retroperitoneal haematoma.

**Diamox (acetazolamide) :** The clinical results with diamox in congestive cardiac failure are conflicting. Banerjee and Chowdhuri<sup>6</sup> tried diamox in 6 cases of congestive cardiac failure with a dose of 250 mg twice daily for 3 days and assessed the diuretic effect by measuring 24-hour urine output. They obtained good response only in one case. Chatterjee and Sen Gupta<sup>7</sup> on the other hand, report of satisfactory diuresis in 4 out of 5 cases of congestive cardiac failure. In one of their cases the oedema persisted in spite of good diuresis. The number of patients studied by them was small. Massumi and Evans<sup>8</sup> treated 27 ambulatory patients with oedema secondary to congestive cardiac failure, for a period ranging from 1½-8½ months. According to them the diuretic response was good except in patients with long-standing recurrent right-sided failure with fixed hepatomegaly. They feel that diamox is a safe and effective oral diuretic. They also noted that premedication with diamox had no potentiating effect on the diuretic action of mercurials and combination of diamox with oral mercurial diuretics offered no advantage over either drug given alone.

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## **CARDIOVASCULAR COMPLICATIONS IN DIABETES MELLITUS—See DIABETES MELLITUS, CARDIOVASCULAR COMPLICATIONS IN**

### **CARDIOVASCULAR PHYSIOLOGY**

*J. C. Sachdev*

Extensive literature has appeared on cardiovascular physiology during the past three to four years and it is impossible within the scope of this contribution to cover the same. An attempt has been made to review briefly the work done in cardiovascular physiology in India only.

#### **Conducting System**

*In the Embryo:* In a 14 mm human embryo it was observed that the sinoauricular node, the auriculoventricular node and the A-V bundle of His were present. Typical Purkinje's fibres were not present in any part of the heart; direct transition of the specialised fibres of the nodes and the bundle into ordinary cardiac fibres was observed<sup>10</sup>. On blocking the activity of the sinoauricular node, the auriculoventricular node becomes the pace-maker. This was done by crushing or clamping the S-A node in anaesthetized dogs. The middle portion of the A-V node has maximum rhythmicity. The rhythmicity of the A-V node varies from 56 to 86 per cent of that of the S-A node in dogs<sup>16</sup>.

*Effect of Hypothermia:* Effects of hypothermia (9-15°C) on electrocardiographic pattern were studied in 15 dogs. On an average the heart beat fell by 6 per min.; five dogs developed complete cardiac arrest out of which three reverted to normal rhythm on rewarming and two died. The P-R interval, QRS complex and Q-T interval increased in duration. Auricular fibrillation, atrial arrest, nodal rhythm, bundle branch block, A-V dissociation, ventricular premature beats and ventricular rhythm were also observed. Widening of the QRS complex to 0.2 second and change of an initial positive T wave to negative denoted serious prognosis<sup>1</sup>.

*Effect of Drugs:* Thiopentone directly decreases the impulse generation in the cardiovascular pace-maker and reduces the force and the excitability of the myocardium. Thiopentone antagonizes the cardio-accelerator and pressor action of adrenaline and noradrenaline. It is due to the potentiation of vasodilator component of adrenaline by thiopentone<sup>5</sup>. Thiopentone has also a mild cardiovagal depressant effect for a period of about ten minutes. It depresses the cardio-inhibitory effect of acetyl choline, the action being more marked in cats than in dogs. Atropine does not reduce the cardio-depressant action of thiopentone but hypotensive action is reduced<sup>6</sup>.

The antimalarials depress the activity of acetyl choline on the cardiovascular system. Quinine and proguanil have been found to depress the pressor effects of adrenaline on the blood pressure and the blood vessels of anaesthetized dogs. On the other hand, chloroquine potentiates this action and this subject deserves further investigation<sup>11</sup>.

#### **Coronary Heart Disease**

In angina pectoris tromexan proved to be a better drug than heparin, because it increased the coronary blood flow considerably, associated with a stimulant action on the heart<sup>2</sup>.

Ballistocardiograms were obtained of 20 normal persons and 20 cases of coronary heart disease before and after smoking, at five minute intervals upto 15 minutes. Seventy-five per cent of the normal subjects did not show any change, while 85 per cent of the coronary cases showed abnormal changes after smoking; it has been suggested that such patients should give up smoking<sup>3</sup>.

#### **Enzyme System in Heart Muscle**

Out of fourteen amino acids, l-isoleucine and l-valine have been found to undergo oxidative de-amination both in the heart and the lung tissue of rats, d-histidine hydrochloride in heart



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tissue and d-isoleucine, dl-isoleucine and l-valine in the lung tissue only. The de-amination of l-isoleucine and l-valine by the heart and the lung tissue was inhibited by hydrocyanic acid and actyl alcohol. The heart muscle was found to contain dehydrogenase or an oxidising enzyme which attacked cystine hydrochloride without causing any formation of ammonia<sup>4</sup>.

### Vascular Physiology

Rabbits were fed with stock diet plus 0.5 g of cholesterol in 5 c.cm olive oil daily for a period of twelve weeks. They were divided into four groups and were observed for a further period of four weeks. Group I remained on stock diet, Group II on desiccated thyroid, Group III on parenteral ovocyclin P and Group IV on both, desiccated thyroid and ovocyclin P. It was found that combination of thyroid and oestrogen therapy yielded better results on regression of atherosclerosis<sup>12</sup>. The concentration of total plasma cholesterol, cholesterol phospholipid ratio and the arterial blood pressure are the important factors involved in the deposition of atheromatous material in the arterial wall. It has been found that Sf 10-20 class and Sf 20 to 100 class of lipoproteins are frequently associated with atherosclerosis. Standard Sf 0-12 and standard Sf 12-100 bodies are significantly higher in coronary disease than in normal. Patients with coronary disease have greater beta cholesterol fraction than normals. After injection of heparin there is decrease in the lipoproteins of higher Sf class and a concomitant increase in the concentration of lower Sf class. There is a tendency for the circulating heparin to decrease with age and in patients with myocardial infarction. Perhaps because of the presence of oestrogen in females<sup>13</sup> the incidence of coronary atherosclerosis is much less in them.

The effects of feeding cocoanut and ground nut oils, cholesterol alone, and in combination with the above, for 10 weeks, on atheroma formation in rabbits were studied. Cocoanut oil caused slight increase of serum alpha and beta globulin, with increase in alpha lipoprotein. Ground nut oil gave similar results but caused an increase of beta lipoprotein. Cholesterol alone and in combination with the above oils, showed progressive increase of serum alpha<sub>2</sub> and beta globulins together with marked increase of beta lipoproteins. It was found that a marked lowering of the ratio of the alpha O-1 beta lipoprotein is related to atheroma formation<sup>14</sup>. Further experiments were done on rabbits who were fed on fat. The occurrence of pulmonary lipidosis in the majority of the oil-fed animals and deposits in the myocardial connective tissue in some animals may be due to phagocytosis of oil globules by mononuclear cells and histiocytes in the lung and the heart. Lipid infiltration observed in two animals might be due to failure of liver to dispose of excess of fat. The contents of cholesterol differ quantitatively in different segments of the arterial system. This may be the cause of appearance of atherosclerosis initially in certain parts<sup>15</sup>.

Administration of argemone oil by mouth produced hyperaemia in the capillaries and venules of internal organs<sup>7</sup>. Capillary reaction can also be produced by painting argemone oil on rat's skin. On oral administration it did not produce any inflammatory reaction, while injection produced severe inflammatory reaction<sup>8</sup>. When argemone oil is injected into the skin of rat it produces capillary reaction at the site but not elsewhere. This reaction was similar as produced by injection of oil. Other edible oils failed to produce such reaction<sup>9</sup>.

It was observed that engorgement of cervical veins was more due to increased vasomotor tone rather than to increased blood volume in the veins. This increased tone could be abolished by ganglion-blocking agents, thus reducing the load on the failing heart. The time required to produce the desired effect varied from person to person<sup>18</sup>.

Poddar has outlined a method for showing the intricate structure of the vascular pattern, with reference to study of the renal circulation by corrosion technique. Vessels are injected with castor oil-celloidin mass. Castings are made of this mass when corroded from soft tissue<sup>20</sup>.

Partial ligation of the vena cava above the hepatic veins is followed by ascites. Incomplete ligation of the portal vein alone or of portal vein and inferior vena cava below the hepatic veins only occasionally results in appearance of small amount of ascitic fluid. This ascites is not permanent<sup>17</sup>.

In fifteen males and ten females suffering from essential hypertension it was observed that the mean sodium level was  $301.8 \pm 5.1$  mg per cent in males and  $312.8 \pm 4$  mg per cent in females. Serum potassium level was  $21.4 \pm 0.7$  mg per cent in males and  $20.5 \pm 0.7$  mg per cent in females. 17-ketosteroid excretion in the urine was  $11.85 \pm 1.4$  mg in males and  $5.49 \pm 1.4$  mg in females. No correlation between adrenocortical function tests and congestive cardiac failure could be established in these cases<sup>19</sup>.

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## CARDIOVASCULAR SYSTEM, SYPHILIS OF

L. K. Ganguli

**Abdominal Aneurysm** : Aneurysm of the thoracic aorta in the majority of cases is of syphilitic origin. Syphilitic involvement of the abdominal part is rare. According to Kutumbia and Thomas<sup>1</sup> the ratio of thoracic to abdominal aneurysm is 4.8:1. In a series of five cases of abdominal aneurysms studied by them, 3 cases were of syphilitic origin, though serodiagnosis was positive in only one case. They are of the opinion that factors like the age, anatomic location, size and histologic changes are to be taken into account to arrive at the aetiology, even when serology is negative or doubtful. In an analysis of 107 cases of aneurysm of the abdominal aorta Wright et al.<sup>2</sup> found serologic or other evidences of syphilis in only 4 cases. From the point of view of aetiology therefore, involvement of the abdominal aorta by syphilitic process is very rare and is not as high as 25 per cent as is mentioned by other workers.

**Diagnosis of Syphilis of the Cardiovascular System** : Clinical and laboratory diagnosis of syphilis is sometimes conflicting. Wasserman or Kahn tests employed for the establishment of syphilis as the aetiological factor are not always conclusive. Friedman and Olansky<sup>3</sup> have suggested the use of treponemal immobilisation test, which according to them is a more valuable laboratory aid to detect the presence of syphilis.

**Penicillin Therapy** : Treatment of cardiovascular syphilis as prescribed by the W.H.O. consists of 600,000 units of PAM daily for 8 days (total 4.8 mega units). For the purpose of evaluation of the efficacy of such a regime Chand et al.<sup>4</sup> have followed 41 cases of cardioaortic syphilis for 7 years. They assessed the progress by comparing the degree of general improvement and changes in the cardiac, radiological and serological status, before and after treatment. They have concluded that penicillin therapy as advocated by the W.H.O. does not prevent the progression of cardiovascular lesions due to syphilis. There is little improvement in cardiac signs and no improvement at all radiologically.

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## CARDIOVASCULAR THERAPEUTICS

R. B. Arora

The heart is a remarkable organ, one which never rests, and one which must accommodate itself to a variety of strains produced by the variation in function and integrity of the vascular system and blood. The heart may encounter difficulties due to injury to the valves, impairment of musculature or disturbances in the conduction system. In the damaged heart there may be disorders of the rhythm and usually an enlargement and dilatation of the chambers. When the heart rate becomes excessively rapid or excessively slowed, its action is much less efficient, and when the ventricles reach a stage of fibrillation it cannot function.

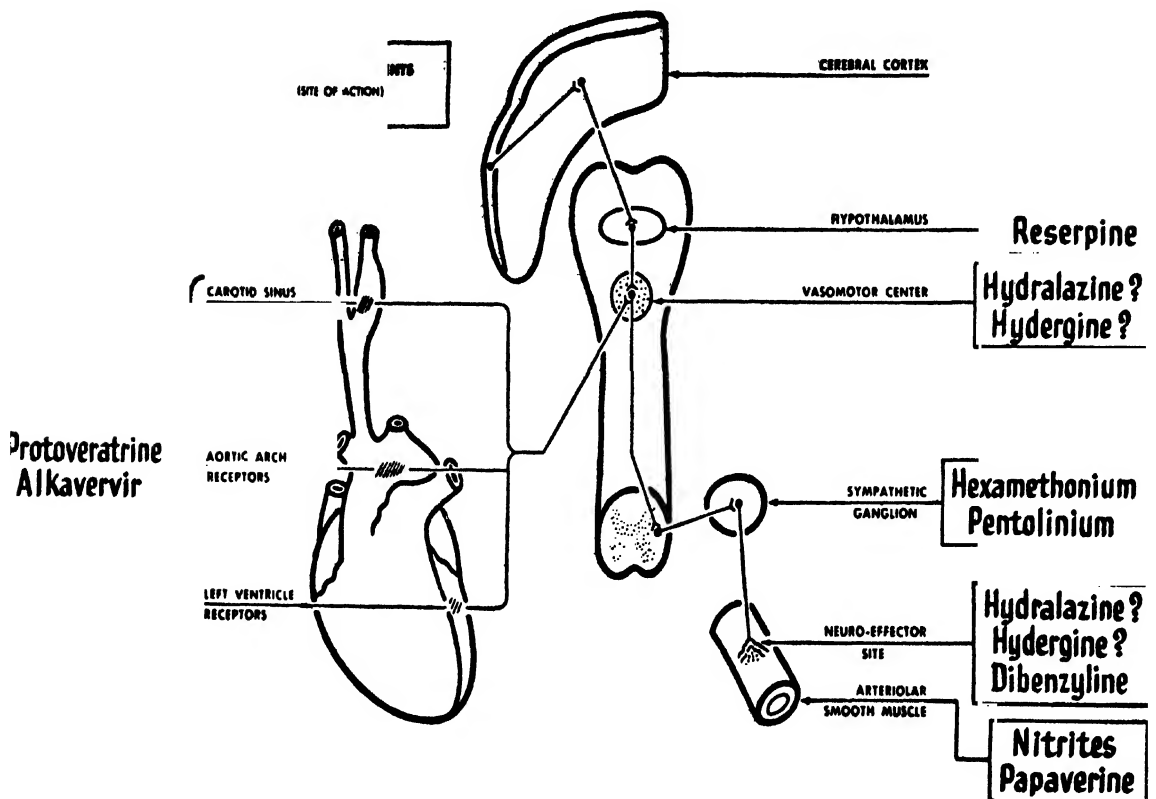
## Cardiovascular Therapeutics

Elevation of the blood pressure may occur in a variety of situations ; in most cases the aetiology is unknown. This ignorance of cause has not hindered the use of numerous drugs in treating the effect. Out of the many types of vascular diseases which affect vessels of different calibre and in different areas of the body, coronary heart disease is the commonest and the most important.

A large number of drugs have as their major pharmacological action the ability to alter cardiovascular function. The object of this manuscript is to describe briefly, the recent advances in the field of cardiovascular pharmacology.

**Hypertension.**—In recent years, a large number of hypotensive drugs have been tried with varying degrees of success. Many of these substances are not easy to use because of the possible dangers attendant upon the administration of each. At the present time, the ganglionic blocking agents, Rauwolfia serpentina, veratrum alkaloids and hydralazine demand consideration.

Results with thiocyanates, dehydrogenated alkaloids of ergot and soluble bacterial pyrogens do not appear to justify their retention in the therapeutic armoury of hypertension, although occasional successes have been claimed for them.



(From *The Heart Bulletin*, Vol. 4, No. 4, 1955. Benedict E. Abreu & Carl A. Bunde.)

**Ganglionic Blocking Agents:** Fall of blood pressure is brought about by these drugs due to interruption of sympathetic vasoconstrictor nerve pathway at the synaptic junction (Moe and Freyberger ; Paton, 1951, 1952, 1954).

**Hexamethonium:** Harrington and Rosenheim (1954) have shown the beneficial effects of this drug alone and in combination with 1-hydrazinophthalazine (Perry et al, 1954, 1955) in severe arterial hypertension. These studies demonstrate the possibility of control of severe hypertension, with normal activity, for a year to 36 months. Postural hypotension and symptoms due to parasympathetic ganglion blockade are the untoward side reactions encountered.

**Pentolinium :** As compared to hexamethonium, it is more potent and its effects last longer. Daily oral dose is 20 mg. It may have to be increased as tolerance develops to it (Grimson, 1955 ; Smirk, 1954, a, b).

**Ecolid :** The actions of a new series of bis-quarternary tetrachloro-iso-indolines have been studied by Plummer et al (1955), who selected ecolid (100 mg orally) for clinical investigations. They claim it to be more potent than pentolinium. But it is too early to assess the results of these therapeutic trials.

**Azamethonium :** It resembles hexamethonium in its pharmacologic response (Bein and Meier, 1950 ; Bernsmeier et al, 1951). It leads to the development of tolerance rapidly (Smirk, 1952). It does not seem to offer any advantage over hexamethonium (Robson and Keele, 1956). Ganglionic blocking drugs have been used to achieve dry operative fields (both to reduce bleeding and to enhance visibility) in neurosurgical and cardiovascular operations (Enderby, 1950, 1954 ; Paton and Zaimis, 1952 ; Scurr, 1955). The degree of hypotension necessary to reduce bleeding is variously estimated. But most anaesthetists aim to reduce blood pressure to 60-80 mm Hg (Little, 1955). Intravenous infusions of Arfonad (a thiophanium derivative) are regarded more satisfactory to achieve this result than hexamethonium (Magill et al, 1953 ; Anderson and McKissock, 1953 ; Scurr and Wymann, 1954). Arfonad is usually given as 1 : 1000 solution i.v. at initial rates of 1-5 mg/min. ; the rate subsequently is varied depending upon the response of the patient.

Procaine amide has also been used in combination with hexamethonium because it enhances the hypotensive effects of the latter (Mason and Pelmore, 1953). This potentiating effect has been attributed to the ability of procaine to cause ganglionic block by inhibiting the release of acetylcholine at the termination of preganglionic neurones.

**Rauwolfia Alkaloids :** Since times immemorial *Rauwolfia serpentina* has been used in the Indian system of medicine. Chopra et al (1933), reported the hypotensive activity of material obtained from this plant. The literature on *rauwolfia* has been reviewed by Vakil (1955). Moyer et al (1955) conducted a comparative study of different extracts of *rauwolfia*. The extract of *Rauwolfia serpentina*, when administered as the sole therapeutic agent, provides a safe and relatively effective treatment for mild uncomplicated hypertensive cases. In addition to lowering blood pressure, there is effect on the psyche, with decrease in tension and aggressiveness, which may help patients make a more satisfactory adjustment to their environment. The commonest side effect is nasal congestion.

Final word as yet cannot be said regarding the mechanism of action of *R. serpentina*. However, there are strong indications that the blood pressure lowering effect of *rauwolfia* drugs principally reflects action at the hypothalamic site, the decrease in peripheral pressure resulting not from a significant alteration of cardiac output but from peripheral vasodilatation consequent on central diminution in sympathetic predominance (Beckman, 1954).

**Veratrum Alkaloids :** Treatment of hypertensive emergencies has been tried with veriloid in oil intramuscularly (Ford et al, 1954). Adjustment of the dose is little difficult but fairly reproducible results can be obtained in individual patients. Although the onset of action is slower with aqueous veriloid intravenously, constant supervision is unnecessary during administration of the oily preparation and fewer injections are required than is necessary with intramuscular injections of aqueous preparations (Harrison, 1955).

**Combination Therapy :** The most satisfactory medical treatment of hypertension would appear to lie in the simultaneous administration of two or more of hypotensive drugs, combined with a low salt regime. Hypotensive agents which act in different ways have a cumulative effect in reducing the blood pressure. Smaller doses, which do not cause serious side effects may therefore, be as effective in combination as a larger dose of a single drug. In this way, the problem of approximation of the toxic and therapeutic dosage, which so often limits the usefulness of these substances, when given alone, may be avoided (Maclean, 1957).

**Coronary Heart Disease.**—In recent years the therapeutic considerations in the treatment of coronary heart disease include the use of anticoagulants and antiatherogenic compounds.

**Anticoagulants :** Evidence has been adduced to show that anticoagulants may prevent the extension of coronary thrombosis and lessen the incidence of thrombo-embolic phenomena.

**Heparin :** It acts as an antithromboplastin and inhibits the conversion of prothrombin to thrombin (Walton, 1955). The dosage employed is 10,000—15,000 units intravenously ; it is

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repeated every eight hours in order to maintain a coagulation time of more than 15 minutes. Long-acting preparations have also received trials by various workers (Loewe and Rosenblatt, 1944 ; Vorgimes et al, 1948).

Clinical trials have also been conducted with heparin analogues. The anticoagulant action of Paritol (alginic acid sulphate) has been observed by Wright (1953). It is very toxic. Treburone (pectin sulphate) acts as an antithrombin and is one-third as potent as heparin. It is given by intramuscular route and has very little toxicity. The duration of action is four hours.

Therapeutic trials with dextran sulphate, a substitute for heparin, have also been reported (Ricketts et al, 1953).

Other anticoagulants used in clinical practice belong to the series which inhibit the synthesis of Factor VII and prothrombin. They include ethyl biscoumacetate (Tromexan), phenylindanedione (Dindevan), Cyclocumarol and Dipaxin. The therapy with these drugs aims at the maintenance of prothrombin time at the level of two and a half times that of the normal control.

**Tromexan :** This drug produces its anticoagulant action in 24-36 hours and which lasts for 24-36 hours after the discontinuation of therapy. Oral dose is 1200 mg on the first day, 900 mg on the second day followed by a maintenance dose of 150-300 mg daily according to prothrombin index.

**Dindevan :** It is given orally in an initial dose of 150-300 mg followed by a maintenance dose of 25-150 mg daily, in divided doses. Onset of effective action is in 24-36 hours and the effect lasts for 2-4 days after the cessation of therapy (Preston et al, 1952 ; Toobey, 1953).

**Cyclocumarol :** This compound was first studied in animals by Scheel and his associates (1949) and in man by Battle and his co-workers (1950). The drug is two to three times more potent than dicoumarol. Optimal reduction in prothrombin activity occurs in 24-36 hours and the effect lasts for 4-14 days after the cessation of therapy. The initial dose is 100-200 mg. The maintenance dose is 12.5-50 mg every one to four days. Cyclocumarol is a new agent and more clinical experience is needed on which to base a sound estimate of its therapeutic value and safety.

**Dipaxin :** It is the most powerful anticoagulant drug known (Field et al, 1955). Initial dose is 20-25 mg orally ; maintenance dose is 2-5 mg daily. The drug is claimed to be of special value in the long term maintenance therapy of patients with thromboembolic diseases (Pascale and Olwin, 1954).

Other anticoagulants used in clinical practice include Warfarin (Pollock, 1955), Marcoumar (Bourguain et al, 1954) and Sinthrom (Schilling and Kruesi, 1955).

With the use of anticoagulants for the prevention of extension of coronary thrombosis, heparin is given on the first two days. Dindevan and Tromexan are also started as soon as possible. The prothrombin time is maintained at two and a half times the prothrombin time of a normal control. The efficacy and reliability of anticoagulant therapy carried out in this manner have been reported from numerous sources (Wright et al, 1948 ; Gilchrist and Tullock, 1954). In spite of severe criticism from some authors, the available evidence seems to justify their use.

**Anti-arteriosclerotic Agents :** Since hypercholesteremia has been alleged to be a factor in the pathogenesis of arteriosclerosis, a number of drugs have been tried to lower serum cholesterol level. Lipotropic substances as choline, inositol, methionine and betaine, alone or in combination, are used for mobilizing lipids from tissues and to hasten the hepatic clearance of these lipids (Drill, 1954). Their use is reported by Davidson, (1951), Morrison (1951) and Greenberg and Bruger (1952). Sitosterol and dihydrocholesterol have also been employed for reduction of serum lipoproteins (Wilkinson et al, 1955). Thyroid and oestrogens have also the potency of reducing serum lipoproteins. However, it should be emphasised that there is no authentic proof that anti-atherosclerotic agents prevent or reverse the atherosclerosis in man.

**Cardiac Arrhythmias.**—By and large, the treatment of arrhythmias is symptomatic. If they cause no trouble, they ordinarily require no treatment (Katz, 1952). A number of drugs, unrelated chemically or pharmacologically, have been investigated in recent years and found to be more efficacious experimentally in their arrhythmia-combating properties. They include chloroquine, camoquin, pamaquin, primaquin, ajmaline, serpentine, Nardostachys jatamansi, chlorpromazine and local anaesthetics (Arora and Madan, 1955, 1956 ; Arora, Sharma and Madan, 1955, 1956). It will be interesting to find their behaviour in the hands of the clinician.

At present, the most effective specifically antiarrhythmic drugs in the treatment of aberrant cardiac rhythm are procaine amide (chiefly for ventricular extrasystoles), quinidine and potassium salts (chiefly in digitalis-induced extrasystoles). Occasionally, digitalis abolishes premature beats (Farah, 1945).

**Procaine Amide (Pronestyl):** It is effective in the treatment of various cardiac arrhythmias, especially ventricular premature beats and ventricular tachycardia (Kayden and Steele, 1951 ; Berry et al, 1951 ; Pascale et al, 1954 ; Szekely and Wynne, 1954). It is not affected by the procaine-esterase of the body and is stable in the duration of its action. It can be given orally or intramuscularly and in an emergency may be injected in the vein.

Like quinidine, it acts by depressing myocardial excitability (Wedd et al, 1951 ; Woske et al, 1953). It raises the ventricular threshold to stimulation, prolongs ventricular conduction and lengthens the refractory period. Haemodynamic studies indicate that the drug reduces the cardiac output and the pulmonary artery pressure and slows the velocity of blood flow (McClen-den, 1951). The usual dose is 0.5 to 1 g. The side-effects due to the drug include nausea, vomiting and marked fall of blood pressure (Stearns et al, 1949). Maintenance therapy is not very desirable because agranulocytosis has been reported in some cases with fatal consequences (Inonye et al, 1951). Ventricular tachycardia is occasionally induced and rarely, ventricular flutter or fibrillation (Daines and Hecht, 1951 ; Read, 1952 ; Schreiner and Kelley, 1952).

**Quinidine:** In spite of its potential toxicity, quinidine still continues to occupy an important place in the drug therapy of cardiac arrhythmias. It deserves mention here that Freedman et al (1956) recently reported a patient in whom haemolytic anaemia as well as, thrombocytopenic purpura occurred following administration of quinidine. No precise explanation has been offered to explain this rare phenomenon.

The question of whether to attempt conversion of auricular arrhythmia after successful digitalization has been controversial on the basis of a recent survey of 74 hospitalized patients who were put on quinidine therapy.

**Potassium Salts:** Potassium salts are often effective in controlling extrasystoles, especially those due to digitalis toxicity (Enselberg et al, 1950). The dosage is 2 to 4 g three or four times daily by the oral route.

**Sodium Lactate:** Of late, observations have been made in the cardiovascular effects of sodium lactate. Bellet et al (1956) found that it is well-tolerated in patients with severe myocardial damage and may give rise to occasional extrasystoles. In patients with partial A-V heart block, sinus bradycardia and complete A-V block, it significantly increases the auricular and ventricular rates. It restores ventricular beating during repeated episodes of cardiac standstill in Stokes-Adams seizures (Bellet et al, 1955). The mechanism by which sodium lactate exerts its beneficial effect is not understood. The most favoured possibility is that it induces alkalosis (Swash and Wallace, 1956). This results in an increase of myocardial excitability and conductivity. The dose employed ranges between 200 ml and 600 ml of M/6 sodium lactate, repeated at intervals depending upon the severity of the symptoms and response of the patient. Storstein and Tveten (1955) advocate making trial with quinidine exclusively, irrespective of circumstances even if there is auricular dilatation, some degree of failure and history of embolic episodes. This evidence, however, cannot be finally assessed as yet in view of the fact that the study was confined only to a small number of cases.

**Ambonestyl:** Preliminary reports indicate that this drug, administered intravenously in 0.5 g doses at 10-minute intervals, suppresses premature ventricular contractions and bigeminal rhythm (Clark and Etsten, 1955). It is claimed to have advantage over procaine amide and quinidine in the absence of depression of cardiac conduction and lack of serious hypotension on intravenous administration. These advantages suggest that ambonestyl might be particularly useful in treating ventricular arrhythmias in patients with conduction disturbances, in controlling arrhythmias during anaesthesia and in cardiac surgery.

**Indigenous Drugs:** Nardostachys jatamansi (fixed oil as well as essential oil), essential oil of Acorus calamus, rauwiloid and reserpine have been shown to be effective in combating experimental cardiac arrhythmias. In addition these drugs exhibit potent antiveratrinic activity. Rescinnamine, however, has been found to be ineffective in combating experimental cardiac arrhythmias ; furthermore, it exhibited weak antiveratrinic activity (Madan, B. R., Master's thesis, Rajputana University, 1957). A ketone isolated from the essential oil of Nardostachys

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jatamansi has been found to possess an activity which is comparable to quinidine in combating experimental cardiac arrhythmias, particularly in ventricular tachycardia following aseptic coronary ligation in the dogs (Arora et al, unpublished observations).

**Tranquillizing Agents:** The concept of unity of fundamental mechanisms of excitation have been emphasized by Harris and Kokernot (1950), since dilantin and phenobarbital have proved to be effective in suppressing the discharge of ectopic impulses in acute myocardial infarction. Further they suggested that preparations with ectopic rhythms might be valuable for preliminary testing of drugs for antiepileptic activity. With this end in view and considering the psychosomatic basis of cardiac arrhythmias, tranquillizing agents were investigated for their suppressor effect in ventricular ectopic tachycardia following acute myocardial infarction. Benactyzine, rauwiloid, chlorpromazine and meprobamate (Arora et al, unpublished observations) have been found to be effective in combating this arrhythmia ; in addition these compounds possess an antiepileptic action. Reserpine is ineffective in combating this arrhythmia and it exhibits no antiepileptic action. This correlation of antiveratrinic and antiarrhythmic actions and antiarrhythmic and antiepileptic actions, outlines the similarities of reactions of skeletal muscle, cardiac muscle and the nerve.

**Hypothermic Ventricular Fibrillation:** Ventricular fibrillation constitutes a major cause of death during hypothermia. Swan et al (1953) proved the efficacy of intra-arterial injection of potassium, in combating this arrhythmia in dogs. Covino et al (1955) showed the protective action of intravenous dacorene against the occurrence of ventricular fibrillation during hypothermia in dogs.

**Heart Failure.—Acetyl Strophanthidin:** Gold and Modell (1948) suggest the use of this drug in sudden heart failure. The route of administration is intravenous. Maximum effects are observed in 10-15 minutes and the duration of action is four hours. However, the advantages claimed with this preparation are disputed by Saloff et al (1956) and Lown and Levine because the toxic side effects observed are not responsive to any therapy.

**Acetyl Digitoxin:** Brill et al (1956) claim this preparation to be better than digitoxin. It is less toxic and the toxic effects are easily amenable to treatment. The dose recommended is 0.8 mg orally followed by 0.4 mg repeated twice at 2-hour intervals. Thus, total digitalization is achieved within 6-8 hours of the commencement of therapy. Average maintenance dose is 0.15 mg daily.

**Acetazolamide (Diamox):** Its use as a diuretic has been reported by Mosley and Barody (1955). It is a carbonic anhydrase inhibitor and produces diuresis by altering acid-base equilibrium. The usual dose is 0.25-0.375 g once daily, preferably by mouth. The toxic side-reactions are frequent and include anorexia, nausea, vomiting, drowsiness, numbness, tingling, dizziness, fatigue, etc. Agranulocytosis and hypersensitivity reactions have also been reported (Pearson et al, 1955).

**Peripheral Vascular Diseases.—Adrenergic Blocking Agents:** One of the recent advances in the cardiovascular system includes the treatment of peripheral vascular disorders by adrenergic blocking agents. Priscoline (2-benzylimidazoline hydrochloride) is effective in increasing the circulation to the limb by relieving vasospasm—normal or abnormal. The increase in blood flow occurs in skin and subcutaneous tissues while there is decrease in blood flow through the muscles (Murphy et al, 1950). It has been tried in Raynaud's disease with encouraging results. Arterial and venous occlusive vascular diseases associated with vasospasm are also relieved by this drug. The drug is given orally or parenterally and intra-arterial use has also been described (Lippmann, 1952). Side reactions like chilliness, pain in the epigastrium, nausea, vomiting, flushing of the face, tingling and tachycardia limit its frequent use.

**Dibenzylamine:** This drug is still under trial and appears to be useful in some cases of causalgia (Moser et al, 1953) and Raynaud's diseases.

**Hydergine:** It is a combination of dihydro-ergocornine, dihydro-ergocristine and dihydro-ergokryptin. It appears to be useful in the treatment of ulcers and gangrene in thromboangiitis obliterans (Kappert and Hadron, 1950) and also in ulceration and dermatitis due to venous stasis. It is given sublingually or intramuscularly and side reactions are few.

**Azapetine (Ilidar) :** Its usefulness in the treatment of vasospastic disorders has been claimed by Green and Dubose (1954). Further therapeutic trials are awaited to assess its usefulness.

Though recent advances in the field of cardiovascular pharmacology have added several useful drugs in the therapeutic armoury of cardiovascular diseases yet much still remains to be accomplished. Many of these drugs are not easy to use because of the possible dangers attendant upon their administration. An ideal antiarrhythmic drug which will depress ectopic foci, but unlike the present antiarrhythmic drugs, will have no depressant effect on nodal tissues, is yet to be found. The solution of these and other related problems require an untiring search for drugs with better therapeutic efficacy and with minimum side effects.

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## CATARACT, SURGERY OF

H. D. Dastoor

This discussion is not as regards the congenital or juvenile cataract but concerns mostly with the senile variety. The most important consideration from the point of view of the patient is when to operate. The period of waiting common in former times till the cataract was fully mature for an operation is not necessary these days. The main consideration is how far the patient is handicapped in his work and in carrying out his daily routine. This arises when the immature cataract is present in both the eyes. Under such circumstances, howsoever the cataract may be immature, at least it is extracted from one eye so as to enable the patient to resume his routine work.

Along with the ensuring of safety of the operation, the ease and comfort of undergoing the same has been very well achieved these days. In Western countries the majority of intraocular operations, including those for cataract extractions are being done under a general anaesthesia, mostly with intravenous sodium pentothal. However, very effective sedation along with general and local akinesia has been achieved, especially with a pre-operative intramuscular injection of a judicious combination of pethidine with chlorpromazine. Besides producing a very effective general akinesia with sedation, the patient though awake and conscious does not experience the slightest pain or discomfort during the whole operation as well as, during the post-operative period. A further advantage is achieved in removing the fear-factor as well as, most effective suppression of nausea and vomiting, which is so essential in eye surgery, especially that of cataract. Precautions against sepsis are well-achieved not only by eliminating any general, focal, or local septic conditions but also with the administration of the modern antibiotics as prophylactic measures. Local anaesthesia is effected with instillation and retrobulbar injection in the region of the ciliary ganglion. Perfect akinesia of the orbicularis muscle is most essential to ensure against tight closure or squeezing of the eye lids and is well obtained by injecting into the branches of the seventh nerve supplying this muscle. Relaxation of the ocular muscles as well as the general muscular relaxation is obtained these days, mostly in the Western countries, by systemic administration of curare and its preparations. Though not an essential condition to obtain such a complete general muscular relaxation for ocular surgery, it is fraught with some danger of relaxation and paresis of other vital musculature, especially concerned with normal breathing. It therefore requires great care in its administration under proper supervision.

As regards the modern trends in the operative procedure, the eye speculum is replaced by most surgeons by the application of lid sutures clamped to the face-towel. This measure not only

ensures against any inadvertent pressure on the eyeball but it also gives greater facility by providing a wider field of operation. Yet some surgeons who continue the use of eye speculum, prefer to use the self-retaining, self-lifting ones to the old-fashioned conventional types which require in their use the help of an assistant to keep it lifted away from the eyeball. Present day cataract surgery is done with the application of sclero-corneal suture for a firm closure of the wound created with the incision. These sutures are essential safety measures especially in intracapsular surgery, to effect early closure of the wound and to prevent post-operative prolapse of the iris and the vitreous. Their application also provides greater freedom of movements to the patient in the early post-operative period. Different varieties of these sutures are employed by individual surgeons. The commoner ones are those of Maclean's, Stallard's and Lindner's which are pre-placed sutures before the incision is made, thereby requiring great precision in making of the incision preferably with help of using a magnifier-loupe spectacles. The post-placed suture like the "limbal-episcleral suture" is equally effective and easier in its application which is made after making the incision. These sutures may be single or more often multiple, usually from three to five in number. The operation is usually of a "combined-type", viz. with iridectomy, to prevent post-operative prolapse of the iris. The iridectomy is of peripheral small button-hole variety and usually single. The modern operative technique is of the intracapsular type in almost all cases, especially older patients in whom the suspensory lens ligaments are easily friable. The intracapsular technique is mostly performed as the post-operative iritis is most infrequent and the subsequent capsulotomy (needling) is avoided. Many surgeons in the Western countries, as well as, in India perform it with the help of capsule-forceps, though many of them also effect the intracapsular extraction of the lens with the suction-method which has been simplified with the advent of a "rubber-pipette cressiphake". With the cressiphake there are less chances of injuring the lens capsule than with the forceps and it is applicable in all the varieties of cataracts, especially those of the intumescent type where the forceps fails to grip the capsule. Another modern innovation in cataract surgery is the introduction of air into the anterior chamber with a canula attached to a syringe, on completion of the operation and after application of the sutures. This procedure has proved to be of value in restoring the iris and pupil backwards in their proper position, with a quicker re-formation of the anterior chamber. There are some who inject penicillin for aseptic precautions; but the introduction of sterile air gives satisfactory results.

Of late, an acrylic lens is introduced in place of the crystalline lens which is extracted as the cataract. By this method subsequent use of aphakic glasses is avoided and is particularly suitable for unilateral cataract where full binocular vision can then be restored between the phakic and the aphakic eyes. In some cases very good results have been observed whereas few cases have developed an excruciating post-operative uveitis leading to loss of the eye. This gave a setback to this new concept in cataract surgery which in the early few successful cases gave a promising outlook. Since then a modification of such acrylic lenticule has been made so as to insert it in the anterior rather than the posterior chamber, to lodge it between the cornea and the iris. This simplifies its insertion, as well as its subsequent removal if need be. This latest innovation is being tried out with minor modifications as to its size and shape, in different parts of Europe and the results are watched with interest since the perfection of this technique will be of great use not only in cases of unioocular aphakia but also in neutralising major refractive errors and conditions of anisometropia.

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## CENTRAL NERVOUS SYSTEM, HIGHER FUNCTIONS, PHYSIOLOGY OF

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During the last decade our understanding of the higher functions of the nervous system has increased by leaps and bounds. By increasing refinements in electrophysiological techniques, by accuracy of localisation of lesion with Horsley Clarke instrument, and by stimulation of the various parts of the human brain in conscious patients during surgical operations, it has been

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revealed that some of the structures of the central nervous system hitherto considered comparatively unimportant play a significant role in the emotional and functional behaviour of the animals. The work in neurophysiological realm has been seen so varied and the literature so voluminous that it is impossible for me to cover in the short space allotted, a comprehensive review of the subject. I shall merely attempt to review one of the most important recent developments—the role of the reticular formation in the integrative activities of the nervous system.

The understanding of the mechanisms concerned with the maintenance of conscious state in animals and human beings has eluded the anatomist, physiologist, and the psychologist alike. It has not been possible to locate the “seat” of consciousness, if there is any, with any degree of certainty. A new era in this complex field of enquiry could be said to have begun in 1949 with the observation of Moruzzi and Magoun, that stimulation of the brain stem in cats produced changes in the electroencephalogram paralleling arousal from sleep or alerting to attention. The electroencephalographic changes have been variously called “activation,” “desynchronisation,” “EEG arousal” or “blocking reaction”. The effect was obtained from the reticular formation of the pons and medulla mesencephalic tegmentum, dorsal hypothalamus and the ventro-medial thalamus. These areas have been collectively called ascending activating reticular system. French, Amerongen and Magoun have shown that evoked potentials can be recorded from these areas on application of peripheral stimuli to the somatic, visual, auditory, and visceral system, suggesting that the centrally situated areas in the brain stem, functioning as a unit are subject to excitation by peripheral sensory stimuli. Such excitation affects the electrical activities of the cortex and behaviour arousal of animals. The authors believe that this medially mediated mechanisms may play an important role in such physiological reactions to sensory stimuli as awareness of sensation or arousal to wakefulness or alerting reaction. The pathways by which impulses from the reticular activating system reach the cortex were not entirely clear. Brodal and Rossi, by employing retrograde degeneration technique have demonstrated the existence of ascending reticular fibres and obtained information regarding their sites of origin, their length and the types of neurons projecting rostrally. French, Verzeano and Magoun have further shown that sensory stimulation aroused two different pathways, one, classical laterally placed lemnisci and the other, medially placed reticular system. Potentials in the lateral sensory pathways displayed rapid conduction, segregation of modality and discrete cortical projection to primary receiving areas of the cortex. Medially conducted potentials exhibited slower conduction, common transport of all modalities and distribution to wide areas of the cortex by way of the diffuse thalamic projection system. Upon peripheral stimulation, a volley of afferent impulses is conducted simultaneously to the cortex by these two systems. The lateral system appears to subserve perception and discriminative sensory functions while the medial system functions in arousing consciousness or alertness without which sensory discrimination and effective response would be impossible. Considerable support to this view is lent by the effects of destructive lesions on the cephalic portion of the brain stem on conscious state. French and Magoun showed that complete destruction of the reticular activating system in monkeys was not compatible with life. Less extensive lesions resulted in a state of akinesia and hypersomnolence in the monkey simulating coma in man. The electroencephalograms were characterised by hypersynchrony which was not responsive to sensory stimuli. The extent to which the reticular activating system was involved appears to influence directly the degree to which the behaviour and the electroencephalogram of the animals were disturbed. French et al have shown that anaesthetics, ether and phenobarbital sodium, block the impulses over the medial system leaving the laterally conducted impulses unaffected. They believe that depression of activity in the ascending reticular activating system participates to a considerable degree in production of anaesthetic state. It is pertinent in this connection to see how far patients suffering from stupor and coma are referable to lesions in the reticular system. French has studied five patients who had profound alteration in “consciousness” for periods ranging from four to nine months. In three of these patients lesions were so situated as to destroy a major portion of the reticular activating system in the cephalic part of the brain. However, the authors very cautiously state, “These data suggest the inadvisability of considering the reticular activating system as a centre of consciousness or a centre of wakefulness, in that afferent impulses are required to excite it and the manifestations of its activity are expressed only through its influences on other structures and on the entire cortex”.

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The subject is further complicated by the discovery of two other non-specific projecting systems to the cerebral cortex. Penfield, guided by the hypothesis of Hughlings Jackson that an area in the brain must exist separate from the motor and sensory cortex where the highest form of functional integration takes place and wherein the motor and sensory arrangement must be such to form the neural substratum of consciousness, is convinced by his own observation on epileptic discharges, as well as from the studies of the electrical stimulation of the brain in conscious human subjects, that such an area of neuronal integration resides in the brain stem. He proposed the term "centrencephalic system" for this hypothetical system of neurons in the higher brain stem which have equal functional relationship with the two hemispheres and closely inter-related connections with widespread areas of each hemisphere. "Most portions of the brain stem may contribute in some way to normal conscious process at certain times but the indispensable substratum of consciousness lies outside the cerebral cortex, probably in the diencephalon." For further information regarding the centrencephalic system the reader is referred to "Epilepsy and Functional Anatomy of the Human Brain" by Penfield and Jasper.

Morison and Dempsey had previously demonstrated a system of neurons in the thalamus, called intralaminary system, stimulation of which influenced the electrical rhythm of widespread areas of cerebral cortex in cats.

These studies were confirmed and extended by Jasper and Droogleever-Fortuyn who also made the remarkable discovery that bilateral wave-and-spike characteristic of the EEG of petit mal could be produced by stimulation within the intralaminary portion of the thalamus. This gives an idea that this region has something to do with the consciousness, for consciousness is primarily affected in petit mal epileptic attacks.

This projecting system has been named thalamic reticular system. Just like the ascending reticular activating system, thalamic reticular system seems to receive collateral afferent communications from the principal ascending sensory pathways and there are important corticofugal projections into the same system. Regarding the functional significance of the thalamic reticular system, Jasper believed that it might play a regulatory role in the process underlying the production of alpha rhythm. Hans Berger had earlier suggested that the mechanism underlying the alpha rhythm must represent the central regulatory system underlying the process of attention, capable of facilitating specific cortical areas whose activities are momentarily focussed in the attentive process, and inhibiting many other areas of systems of neurons which would otherwise be competing for the "central sphere of consciousness." Jasper believes that the nonspecific thalamo-cortical projection system, with its closely inter-related central reticular network and separate radiating projections which seem to terminate within the layers of the cortex in a manner capable of facilitating, inhibiting, or timing conduction processes in synaptic networks of the more specific functional system, is particularly suited for the performance of such a role. A conjecture is made that this system may be concerned in the central control of affective processes. The activities of the reticular formation themselves may be influenced by cortico-thalamic projections. The possible sequence of events on sensory stimulation according to Fessard would be—sensory projection to the receptive areas through specific pathways; unconscious patterning in the cortex; projection of competitive patterns towards the centrencephalic structures, where interaction would produce a higher degree of integration, this resulting in a new orientation of the selective ascending impulses and eventually in the arousal of integrated response.

Further work on the reticular system has showed that it is connected to the cerebellum (Brodal). It has been shown that it sends fibres to the gamma efferents of the anterior horn cells and thus facilitate spinal reflexes (Granit & Kaada). It has been shown that there is a certain degree of adaptability in the reticular system for auditory stimuli (Sharpless). Indeed, the work on the reticular system has been proceeding at a pace which is in sharp contrast to any clear cut inference which could be drawn regarding its functional significance. One is inclined to ask with Adrian, "Whether we are to regard the reticular system as just coming in to wake us up in the morning and send us to sleep at night, to do non-specific activation, or whether that it has got something to do with the direction of attention with the actual work of the conscious brain?" Opinion on this point is very sharply divided. The temptation to conclude that reticular formation is concerned more than any other part of the brain with conscious processes is irresistible to most physiologists. Lashley however, does not credit this system with such a function. In his view all that can be claimed for the present is that the system may serve as an activating agent or pacesetter for the cerebral cortex. He is supported in this concept by Bremer. According to him it

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is the dynamic integration of all cerebral processes at a single moment which makes consciousness. While it is proved beyond doubt that the brain stem structures have widespread influences on the activities of the cerebral cortex, there are still gaps in our knowledge to be bridged before their true functional significance could be assessed. These gaps as indicated by Bremer are firstly, the relationship between the diffuse or nonspecific thalamic system and brain stem reticular formation and secondly, the functional inter-relations between impulses emitted by the specific sensory thalamic nuclei on the one hand and the diffuse system on the other. I am optimistic enough to believe that it would not be long before these complexities are resolved.

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## CENTRAL NERVOUS SYSTEM, RADIOLOGICAL ASPECTS OF M. G. Varadarajan

**Calcification in the Pineal Body:** Calcification occurs as a normal phenomenon in adults in the pineal body as age advances. The frequency with which calcification is seen radiologically throughout all ages is about 60 per cent. It is seen rarely in the first decade, in about 20 per cent of individuals in the second decade and thereafter it is much more common.

In a study of more than 1000 plain X-ray pictures of the skull, it has been found by Ramamurthi (1957)<sup>8</sup> that calcification of the pineal body is not so common as in the West (10 to 15 per cent throughout all ages).

**Radiological Calcification in Posterior Fossa Tumours** is described by Begg and Robinson (1955)<sup>1</sup> who studied 82 patients with verified tumours. X-ray evidence of calcification was confirmed by microscopic findings in five. Calcification may be detected in X-rays in about 10 per cent of posterior fossa tumours, an incidence similar to that found in tumours above the tentorium. Three types of deposits may be recognised—scattered, curvilinear and homogeneous—each providing information about the character of the lesion. The demonstration of calcium is important not only to indicate the position of the tumour but to suggest its nature. Thus in children, visible calcification probably indicates an astrocytoma or ependymoma and in adults a meningioma. Calcification in a posterior fossa tumour probably excludes a diagnosis of medulloblastoma, haemangioma or neuroma.

**Premature Fusion of Cranial Sutures**<sup>4</sup>: Ramamurthi reviews the knowledge and literature about premature fusion of skull sutures and presents the experience of the neurosurgical unit, General Hospital, Madras, in dealing with such cases. The paper also focuses attention to the fact that the difference between microcephaly and craniostenosis must be recognised and that at different ages and for different symptoms varied surgical procedures have to be adopted to get the best possible results.

In microcephaly the size of the whole cranium and the brain remains small. The sutures of skull bones may or may not be fused. The defect involves both the brain and the skull and hence surgery on the skull will not be of much avail. On the other hand, in craniostenosis, the brain is developing normally but there is premature fusion of one or more sutures leading to a lack of growth in the particular direction, leading to a deformity of the skull and very often lessening of the intracranial capacity. It is in such cases that surgery is of avail.

*X-ray Findings:* These are characteristic and conclusive. Very often, X-ray pictures may give the first indication that anything is wrong with the patient. Depending on the nature of the condition, the size and shape of the skull vary considerably. The striking feature is the "beaten silver" appearance of the calvarium. On careful examination many sutures will be found to be still open. There is platybasia in brachycephaly and a narrowing of the basal angle in typical oxycephaly. The optic foramina are usually normal in size though a decrease in their size has been reported. The orbits are shallow and the orbital roof may almost be vertical. A careful study of the X-ray is necessary before deciding on the correct type of surgical treatment.

Regarding treatment, the author is of opinion that linear craniectomy in childhood and infancy and subtemporal decompression in the older age group serve to relieve the symptoms.

*Experiences with Tuberculomas of the Brain<sup>6</sup>:* Tuberculomas of the brain are some of the commonest tumours of the brain met with in our country. 19.4 per cent of verified tumours of the brain in this series have been tuberculomas (total cases studied 180).

*Plain X-Rays of the Skull,* may occasionally show a calcified area but this is not common even though such a notion is commonly held. Only 5 out of 72 cases showed calcified spots in the plain X-rays. But X-rays of the removed specimens show much more obvious calcification. Ventriculograms do not give any indication as to the pathology of the lesion. Cerebral angiography always shows the lesion to be avascular. An avascular intracranial space-occupying lesion is more likely to be a tuberculoma or a chronic abscess.

*Sturge-Weber Syndrome<sup>7</sup>:* This uncommon, though not rare disease was first described by Sturge (1879) and later by Weber (1922). It is characterised by a triad of symptoms—angioma on the face, epilepsy and congenital glaucoma or buphthalmos. Other associated congenital anomalies like megalocornea, angioma of the retina are also common.

One girl, aged seven, whose plain X-ray of the skull, showed typical parallel calcification. Second case, a girl aged twelve, admitted with a complaint of jacksonian fits, involving the right half of the body, weakness of the right upper and lower limbs and defective vision in left eye; plain X-ray of the skull showed extensive areas of calcification with characteristic parallel or double lines.

The calcification extended from the occipital lobe to the frontal and was confined to the left side. Under anaesthesia, a left side carotid angiogram was done by the open method. This failed to reveal any connection between the cerebral vascular tree and the calcified areas in the brain. But there were other cases where there was definite evidence of angiomata in the cerebral cortex but with no calcification. Cerebral angiography definitely proved the existence of angiomatous malformation.

The third case was of that type. Miss T, aged 7, was admitted with a complaint of jacksonian fits, involving the right half of the body. On examination, she was found to have angiomata on the midline of the forehead, upper lip and palate. Plain X-ray of the skull showed no abnormality and there was no calcification. Left-sided cerebral angiography established the existence of large arteriovenous angiomatous malformation in the left cerebral hemisphere. Hence it was found that calcification of angiomatous malformations may not coexist and different combinations are possible. The authors believe that calcification is only a process of a secondary nature which may start early or late in life and that it is not the primary cause of symptoms of cerebral irritation. There was no calcification in the third case cited, who had typical jacksonian fits. It will be interesting to watch whether she develops calcification after some years.

The authors suggest further studies in cerebral angiography, in cases of Sturge-Weber syndrome by using the cinematographic technique before the last word can be said on the subject.

*Carotid Angiography in Intracranial Lesions<sup>8</sup>:* Total cases studied, 120. Cerebral angiography has now established itself as the most important radiological aid in the diagnosis of a large variety of intracranial lesions, by percutaneous puncture of the carotid artery i.e., percutaneous carotid angiography. Only four cases required the open technique. They

## Central Nervous System, Radiological Aspects of

have outlined the method of puncturing the artery, simple tests to know that the needle is in the lumen of the artery, injection of dye and technique of taking skiagrams. The advantages are that it is not too difficult to perform and it can be repeated as often as necessary. There are no bad after-effects so that the examination can be done on out-patient cases. The pain in the neck and the occasional swelling that occurs disappear in 36 to 48 hours. The examination can be done in any age group. This procedure, in addition to giving an anatomical localisation as to the site of the tumour and its size, reveals also in many cases the pathological nature of the lesion so that surgery and anaesthesia can be preplanned. After treatment, check up as to the recurrence of the growth can also be maintained by cerebral angiography.

Cysts, abscesses and tuberculomata show avascular areas with spreading out of the normal vascular pattern of the cerebral hemisphere. Metastases in the brain from malignant tumours elsewhere in the body are not an uncommon occurrence and cerebral angiography has revealed a number of these cases.

The greatest diagnostic value of this procedure lies in the demonstration of intracranial aneurysms. Subdural haematoma gives a pathognomonic picture of displacement of the vascular pattern away from the calvarium and is best seen in the antero-posterior films. Evidence of bony injury may be seen in the overlying skull bone.

Carotid angiograms are also done as a routine for large pituitary tumours with considerable sellar destruction. The procedure helps to exclude the presence of an aneurysm of the internal carotid artery. It also gives an indication of the exact extent and direction of spread of the pituitary growth, a very important information necessary to plan the mode of surgical attack in pituitary tumours with huge extrasellar extension. The procedure is felt to be less risky than pneumoencephalogram and more informative than ventriculogram in such large tumours. The authors have done so far about 1000 carotid angiograms with no mortality, and with valuable results.

*Percutaneous Vertebral Angiography*<sup>9</sup> was performed in ten cases with successful results. The indications were :

1. In patients who had subarachnoid haemorrhage : (a) if an arteriovenous malformation has been found by carotid angiography and (b) if bilateral examination of the carotid artery is negative.

2. It was also tried as a method of diagnosis in posterior fossa tumours and aneurysms.

3. Cerebellar angioma.

*Ventriculographic Changes in Cysticercosis of the Brain*<sup>5</sup>: Ventriculographic changes in a case of cysticercosis of the brain in a girl aged 12, are described. When the cysts protrude into the ventricles, the outlines of the ventricles show alterations which may help in confirming the diagnosis.

*Radiological Diagnosis of Tumours of Spinal Canal*<sup>2</sup>: The procedure of radiological diagnosis of space-occupying lesions of the spinal canal has been discussed in short.

The advantages as well as disadvantages of various types of myelographies have been enumerated. The various indications for myelography are given and pitfalls are explained. The analysis of myelographic examination done at Irwin Hospital, Delhi, is given. The total number of cases done is 96 during a period of four years with the contrast Medium 'Myodil'. The radiological findings of different types of tumours are discussed and various types are classified according to these findings. An attempt has been made by the author to include skiagrams and illustrations of as many types as possible of these lesions in all segments of the spinal cord.

*Osteoclastoma of the Skull*<sup>10</sup>: It is a rare condition. Only ten cases have been reported in the literature. The authors have added one more case to the literature, of osteoclastoma of the sphenoid bone simulating a pituitary tumour in a male aged 35. The patient complained of headache and gradually increasing dimness of vision in the right eye, of five months' duration and for the last month, he had not been able to lift his right eyelid. On examination, positive neurological findings were: (i) primary optic atrophy of the right and temporal pallor of the left optic disc; (ii) complete loss of vision in the right eye, with contraction of temporal field in the left eye; (iii) limitation of medial and upward movements in the right eye, whereas external rotation of the eye was not limited and (iv) ptosis of the right eyelid. The patient had



also infranuclear paresis of the right facial nerve. Roentgenograms of the skull showed enlargement and erosion of the pituitary fossa.

The tumour was primarily thought to be a pituitary adenoma because of the presenting symptoms, although the facial paralysis could not be explained by this diagnosis. The firmness of the tumour, on palpation during operation, the facial paralysis and the radiological appearances all fitted in with the diagnosis of osteoclastoma and the pathological report confirmed the diagnosis.

*Paget's Disease of the Axis Causing Quadriplegia*<sup>11</sup>: Paget's disease of bone is not a common condition in India. The commonest sites of affections of the spine are the lumbar and thoracic regions, the cervical region being less frequently involved. In the only case reported by Whalley (1946)<sup>12</sup> the atlas and axis were both affected, as well as, the skull and there was an atlanto-occipital dislocation with paraplegia. The points of interest, in the case reported by the authors in a man aged 60, were, localisation of the affection to the axis alone with no other bone of the skeleton involved, the presence of quadriplegia; plain roentgenogram of the cervical area revealed sclerosis of the second cervical vertebra, myelogram after cisternal puncture showed a block at the level of the second cervical vertebra, operation revealed thickening of the laminae of the axis, soft and very vascular, and at autopsy, the axis was enormously thickened and there was a well-marked hump at the level of the axis; the diagnosis was clinched by histological examination of bone.

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#### CENTRAL NERVOUS SYSTEM, STIMULANTS OF

W. R. Bett

*Meratran* : Meratran [alpha-(2-piperidyl) benzhydrol hydrochloride] is a central nervous system stimulant whose action is not unlike that of the amphetamine series. Apparently, however, the drug is not sympathomimetic as it has no marked cardiovascular pressor effects, and it does not markedly interfere with sleep or appetite.

Begg and Reid report their experience with this drug in over 200 psychiatric patients, the majority of whom suffered from depression, and emphasize that Meratran must be used with care. Of 29 patients with the 'purer type of reactive depression' 25 were considerably helped, while only 11 of 22 patients suffering from reactive depression with hysterical features benefited. Endogenous depression was not relieved; some worsening noted in certain patients might have been due to the drug. The most serious drawback to its use was a tendency to exacerbation of pre-existing anxiety, especially as this effect was unpredictable and complications were produced 'more swiftly, unexpectedly, and sometimes more severely than happens with amphetamine'. Combination with chlorpromazine hydrochloride or amylobarbitone sodium will often prevent increased anxiety. The use of meratran is contra-indicated in the presence of severe tension, agitation, or anxiety. Obsessional symptoms may be considerably worsened, especially with larger doses. These authors were 'impressed with its possibilities' in post-leucotomy lethargy.

According to Fullerton, Meratran relieves patients with chronic depression which is reactive in type or is secondary to senile changes. He quotes American workers as reporting that the drug is of value in depression and psychomotor retardation due to mental illness or the side-effects of chlorpromazine and reserpine. Its use is not followed by depression.



## Cerebral Circulation in Health and Disease

**Ritalin:** Ritalin (methyl phenyl piperidyl acetate hydrochloride), a psychoanaleptic drug, was given by Ferguson and Funderburk to 215 women over the age of 60, with various senile behaviour disorders (incontinence of urine, restive behaviour, aggressiveness), either alone or combined with reserpine (Serpasil). Ritalin alone was administered to 62 patients whose behaviour was classified as negativistic. Improvement was strikingly prompt, and it was possible to adjust doses and to supplement one drug with the other. Eventually 195 patients were receiving both drugs which caused a 'marked mental awakening of the patients to the degree that they were better able to participate.' Though drug treatment alone is not enough, it was felt that the combination 'opened an entirely new and most promising approach to the problem.' Neither advanced age nor cardiac disease proved to be a contra-indication.

In the experience of Salisbury and Hare, Ritalin in a self-controlled, double-blind clinical trial at two dosage levels was of no value in the treatment of 48 patients with chronic schizophrenia.

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## CEREBRAL CIRCULATION IN HEALTH AND DISEASE

E. P. Bharucha

The nitrous oxide technique of Kety (1949) has shown that the cerebral blood flow varies from 500-1000 c.cm per minute (average of 750 c.cm per minute), the oxygen consumption is 5.4mg/100 g brain and the brain having an entirely carbohydrate metabolism, has a respiratory quotient of 1.

The cerebral blood flow depends on two factors, the systemic blood pressure and the cerebrovascular resistance. The cerebrovascular resistance varies directly with intracranial pressure and the viscosity of the blood (increased in polycythemia and lowered in anaemia). The most important factor controlling the cerebrovascular resistance is the calibre of the blood vessels. Ever since the demonstration by Penfield<sup>7</sup> in 1936 of intracerebral vascular nerves arising from cervical sympathetic chain, the role of the sympathetic in the regulation of cerebral blood vessel calibre has been a matter of much speculation. They seem to be of negligible importance during health and Harthel<sup>7</sup> has shown that bilateral stellate ganglion block in normal people produces no increase of cerebral blood flow. Though nervous impulses do not alter appreciably the lumina of cerebral vessels, it is well-known that these are chemo-sensitive. Carbon dioxide is a powerful cerebral vasodilator. Inhalation of 7 per cent CO<sub>2</sub> produces 75 per cent increase in cerebral blood flow. Both caffeine and aminophylline decrease the cerebral blood flow (Wechsler et al 1951). Papaverin and nitrites increase the cerebral blood flow. Histamine only increases the cerebral blood flow when the main arterial pressure is not lowered by more than 12 per cent. This also holds for the sympatholytic drugs (T.E.A.B., piriscoline and hexamethonium).

*The Effect of Hypotension, Hypertension and Arteriosclerosis on the Cerebral Circulation:* Hypertension increases the cerebral vascular resistance but only reduces the cerebral blood flow, if it is combined with arteriosclerosis.

In normotensive arteriosclerotics the cerebral blood flow is normal. There are no criteria for the clinical diagnosis of cerebral arteriosclerosis. The diagnosis is always a tentative one, based on indirect evidence viz. systemic and coronary arteriosclerotic manifestations, previous cerebrovascular accidents, retinal arteriosclerosis. Adams<sup>7</sup> has shown atheroma to be rare in vessels which have a calibre of less than 2 mm diameter—the retinal vessels are 1 mm in diameter and therefore are not an accurate reflection of cerebral arteriosclerosis. Hicks and Warren (1951)<sup>4</sup> have shown that on autopsy of 100 successive cases of cerebral infarction no occluding thrombus could be demonstrated in 6 cases. Hutchinson and Yates (1957)<sup>5</sup> have stressed the importance of looking for carotico-vertebral stenosis in the neck in cases of infarction with patent intracerebral vessels. Two mechanisms have been suggested in the production of infarction without thrombosis, spasm and fall in blood pressure.

**Cerebral Spasm :** Many doubt if the cerebral vessels with poor musculature can constrict at all and Pickering (1954)<sup>7a</sup> believes that the transient paralytic episodes in hypertension are due to small thrombi. However, retinal vessels have been shown to go into spasm and experimentally the cerebral vessels of the cat (Forbes)<sup>7</sup> and mouse (Byrom)<sup>7a</sup> have been seen to go into spasm and Ecker has demonstrated spasm on arteriography in many conditions. Cerebral spasm has now been accepted as a cause of transient cerebral vascular episodes.

**Sudden Hypotension :** Some of Hicks and Warren's cases must surely have been examples of infarction as a result of a sharp drop in blood pressure in elderly patients with rigid cerebral vessels. The hazards of sudden hypotension on the brain of elderly patients (to a lesser extent in the young) are being increasingly recognised. Cerebral anoxia can result from hypotension resulting from haemorrhage, peripheral failure (diarrhoeas, pneumonia, myocardial infarction), Stokes Adams syndrome and paroxysmal tachycardia. Cole, and Sugarman, (1952)<sup>3</sup> have described cases of myocardial infarction admitted to hospital with a diagnosis of hemiplegia, delirium tremens, or epilepsy. Apart from frank cerebral infarction, transient or more permanent mental impairment may result from such episodes. Bedford (1957)<sup>1</sup>, has described a series of cases who on recovery from hypotension in pneumonia and severe diarrhoea, became demented, bed-ridden, incontinent, aphasic, unaware of surroundings and unable to recognize people or dress and feed themselves. That fainting is a protective mechanism in cerebral hypotension has been stressed by Bourne, (1957)<sup>2</sup>. Assumption of horizontal posture automatically and mechanically corrects cerebral hypotension when this is prevented as under nitrous oxide anaesthesia in the dentist's chair. Dementia and permanent cerebral damage has resulted. Bourne has collected a series of such cases.

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#### CERVICAL SPONDYLOSIS—See SPONDYLOSIS, CERVICAL

#### CERVIX, CANCER OF

K. Bhasker Rao

Early diagnosis of cancer cervix is essential for improved results in therapy. Vaginal cytologic studies for detection of cervical cancer have been undertaken by numerous workers with encouraging result<sup>1,2,3</sup>. In a series of 2250 patients where no clinical cancer could be detected by the gynaecologist, the cytologist discovered 10 cases, eight of which were of the *in situ* type. The cost of finding a single case of cancer by this method is estimated between 110 to 500 dollars and the time taken for it about 500 hours. The cytologist should be experienced to avoid errors and in all suspected cases biopsy should be done. By direct examination of the cervix with colpomicroscope (magnification 200-250) and ultrapak microscope, with nearly 1,000 times the magnification, cancer can also be detected<sup>4</sup>. The results can be improved by using Papanicolaou's stain or wiping the cervical surface to expose the deeper layers for inspection; the wiped off material may be studied separately under the microscope.

Cancer *in situ* is a condition where the whole thickness of the cervical epithelium is replaced by typical malignant cells without any evidence of invasion of the subjacent stroma. This has to be distinguished from basal cell hyperactivity. Te Linde<sup>5</sup> saw 211 cases of carcinoma-in-situ in 15 years and found that in most cases the lesion became invasive after a varying interval of one to 19 years. It may also be seen at the growing edge of an invasive cancer, or on the other hand, restricting itself to the lining epithelium, it may spread beyond the cervix down to the vagina or it may spread upwards on to the fundus and occasionally become invasive. Ideal treatment in these cases of carcinoma *in situ* is radical hysterectomy and removal of the adjacent parametrium and upper 2 cm of the vaginal cuff.

Choice of therapy in cervical cancer is between radium and surgery, equally good results having been claimed with both. The current trend<sup>6</sup> however, is not to consider one method as the rival of the other but to select each case—depending on the general condition of the patient, the

## Chelating Agents

extent and nature of the growth and the response shown by the growth as well as the host to irradiation. This response has been studied by serial biopsy and histologic changes in the growth, by cytologic changes in the nonmalignant vaginal epithelial cells of the host, by the smear technique<sup>7</sup> or by the cytochemical studies<sup>8</sup> of tumor cells—before and after irradiation. If by any of these techniques, good response to irradiation is seen, this line of therapy is continued to full dosage, and if the response is poor, surgery is indicated. Each case is chosen on its own merits and looked after by a trained radiologist or an expert surgeon.

Radiological methods followed in the radium hemmet<sup>9</sup> give the best results. Intracavitary and special vaginal applicators are used followed by irradiation to the parametrium. The latest 5-year survival rates for stage I and stage II are 89.9 per cent and 52.8 per cent respectively, with the risk of bladder damage at 0.90 per cent. Meigs claims 85-90 per cent (surgery alone) 5-year survivals for stage I with incidence of urinary fistula of about 13 per cent. Advocates<sup>10,11</sup> of the radical vaginal surgery (Schauta's operation) claim 5-year survivals ranging from 50 to 70 per cent ; these results showed the disadvantage of not removing the regional glands. Mitra, now, does extraperitoneal lymphadenectomy with the radical vaginal operation to overcome this defect. Large series of cases without any primary mortality have been reported by all these surgeons, but by the abdominal approach the results have been better except for a higher urinary fistula rate depending on the thoroughness of the operation. In advanced cases, Brunswick<sup>12</sup> has produced 11 five year cures for his first 100 pelvic exenterations but with a heavy primary mortality.

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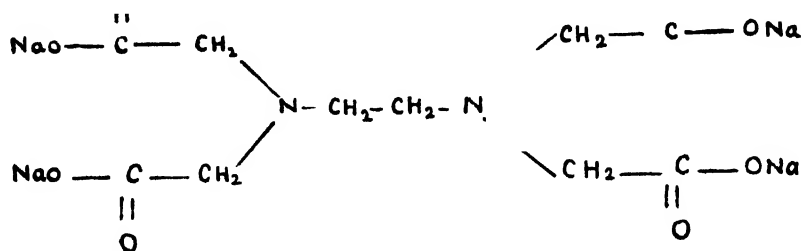
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## CHELATING AGENTS

The word chelate ('chela' meaning claw in Greek) signifies a process by which certain chemicals, metals in particular, are abstracted or 'hooked' or 'clawed' by organic complex compounds, by donating others like oxygen, nitrogen, sulphur. The metals, mostly polyvalent, that are readily chelated include calcium, iron, copper, chromium, mercury, etc. This results in a stable water-soluble but non-ionisable ring structure, in which the metallic iron is firmly bound. The metal however is not precipitated. The chelating agents bear a remote resemblance to ion exchange resins, in action. Chlorophyll and haemoglobin may be said to be natural chelating complexes, while citric, malic, lactic and tartaric acids are the few others.

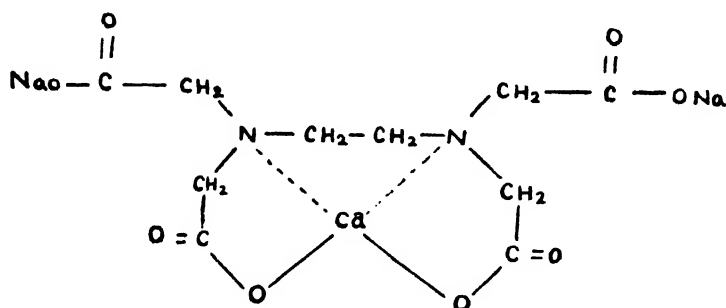
Ethylene diamine tetraacetic acid (EDTA) is an organic molecule capable of forming a complex with metals like calcium. Originally marketed as sequestrene and versene (tetrasodium salt of EDTA), other allied compounds designated nullapons or trilon intended for softening water by abstracting calcium or magnesium or preserving food, chelating agents are now used mainly in lead poisoning and to remove unwanted calcium.

Tetra sodium salt of EDTA has the following structure :



The conception of action of this complex, is as though a ring of atoms possess hooks represented by a special kind of chemical bonds, which 'claw' or 'chelate' some metals. Most metals can be chelated by organic complexes containing nitrogen, sulphur or oxygen, attached to an active hydrogen ion, but the metal itself is attached in a non-ionic form. The metal then loses its usual physical, chemical and pathological properties, and hence the application of the principle of chelation to metallic poisoning.

In animal experiments, EDTA caused tetany leading to fatal hypocalcaemia due to calcium abstraction from the body. When calcium was added to EDTA to form calcium disodium EDTA (CaEDTA) and then administered no hypocalcaemia was noticed, but the complex tended to abstract other available cations, preferably multivalency metals.



Calcium Disodium EDTA (CaEDTA)

**Absorption and Fate :** Experiments with  $C^{14}$ -labelled calcium EDTA had revealed that orally, the complex is not readily absorbed. Intravenously, about 93 per cent is excreted in the urine in 24 hours and the small remaining amount in faeces<sup>5</sup>. Repeated administration leads to depletion of skeletal source of calcium.

**Clinical Application :** When CaEDTA is administered, no other cation of biological importance is involved, but foreign metallic contaminants of the body like copper, nickel, lead, etc., may be abstracted. The complex has been used as food preservative when even minute traces of metals that determine oxidation or deterioration of the food are removed; it is particularly useful in preserving sliced fruits, vegetables, fats and vitamin C compounds.

The main clinical use of CaEDTA is in the treatment of lead poisoning in children and adults. To a less extent it has been used (1) in chromium poisoning, (2) plutonium poisoning, (3) calcium affection of eyes, (4) in hepatolenticular degeneration presumably to abstract copper, (5) as an anticoagulant as a substitute for citrate, and (6) in dissolving urinary calculi, etc.

Foreman et al<sup>4</sup> have reported 60 cases of blood transfusion where EDTA was used as anti-coagulant. They have also reported that EDTA though valuable in dissolving urinary calculi, may damage the mucosal lining of the tract.

Zindahl et al<sup>7</sup> noted that dimercaprol and sodium calcium EDTA induced some improvement in the neurological signs and symptoms of hepatolenticular degeneration with increased excretion of copper. They however felt that combined treatment with ion exchange resins may give better results by abstracting copper in the alimentary tract and preventing their systemic absorption.

Figueroa et al<sup>3</sup> observed that sodium calcium EDTA was of limited use in haemachromatosis and that blood removal or venesection is to be preferred. Maloof<sup>6</sup> reported favourably in chrome ulceration of skin in tanning industry, by the use of the complex. He had used 10 per cent sodium calcium EDTA as an ointment in hydrous wool fat when healing of the ulcer was satisfactory.

Breiner and DeVoe<sup>2</sup> had treated band keratopathy corneal ulceration due to calcium with sodium calcium EDTA and noted some improvement in vision; it had however no satisfactory effect on clearing the scar tissue. The chelate was applied by iontophoresis.

**Lead Poisoning :** The principle of chelation seems to have been applied to the best advantage in lead poisoning. Bidstrup<sup>1</sup> has ably reviewed the entire use of chelating agents.

## Chemotherapy Retard of Leprosy

When calcium EDTA is administered to cases of lead poisoning, calcium is displaced by lead as the binding power of lead is stronger than calcium. The lead chelate thus formed is soluble but lead cannot be ionised and thus rendered inert. This method therefore, is deemed superior to the earlier ammonium chloride or potassium iodide treatment.

Calcium EDTA is administered here in 1 g doses diluted with 200 c.cm of 5 per cent glucose as drip, twice a day. This may be continued for 3 to 5 days. The compound is available in 5 c.cm ampoules of aqueous solution containing 1 g. Bidstrup<sup>1</sup> recommends a maximum of 5 g per 30 pounds per week and never in a higher concentration than 3 per cent.

Most physicians experienced in this treatment agree that clinical improvement in acute cases is impressive and in chronic cases satisfactory. In lead encephalopathy in children, response is said to be striking (Wade and Burner, 1955; Giles Moore and Still, 1955; Travers, Rindle Short and Harvey, 1956).

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## CHEMOTHERAPY RETARD OF LEPROSY

R. Subramaniam

This article is published in French. Lauret et al are doing leprosy control work in West Africa. They are suggesting a method by which patients can be attended to at long intervals and at the same time effectively. Where patients are able to come to the clinic once or twice a week, they prefer oral treatment. They consider chaulmoogra injections as a valuable adjunct in the treatment of tuberculoid and indeterminate cases. But in fields where patients are likely to be seen at longer intervals, once in a month or once in 15 days, they advocate D. D.S. by intramuscular injection and they consider that its retard therapy has valuable success in these cases. They have used chaulmoogra as the menstruum. The ethyl esters (with 4 per cent guaicol) have been the vehicle of choice. It contains 1.25 g of D. D.S. in 5 or 6 c.cm. It was observed that a single injection will maintain an adequate sulfone blood level for 15 days or more. Fifteen-day interval treatment gave excellent therapeutic results especially in advanced forms of the disease. Reactions are less important and less frequent than with oral treatment. The authors also tried Floch's suspension in 0.2 per cent agar-saline and found that it gave an even better retard effect than the chaulmoogra esters but the salt has a flocculating effect on agar and after some months there is formed an irreversible coagulum which is impossible to inject. It is concluded that the semi-monthly injection of 1.25 g of D. D.S. in chaulmoogra ethyl esters constitutes the most practical treatment for patients coming from long distances. It is particularly effective in lepromatous cases and is without danger and is easy of application.

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## CHEST, SECTIONAL RADIOGRAPHY OF—See RADIOGRAPHY OF THE CHEST, SECTIONAL

## CHILD AND ADOLESCENT HEALTH

A. K. Niyogi

*Prematurity and Development at Childhood Ages*: Douglas investigated the late effects of prematurity in 407 children of eight years in the U. K. He found that the legitimate single born child weighing 5½ lb or less at birth, when compared with normal controls, was found handicapped in tests done by reading, vocabulary and intelligence but the difference was quite small. It was however found that there was a small group of premature children with no obstetric or genetic explanation of their low birth weight, who showed outstandingly poor scores. The controls were fixed on the basis of sex, ordinal position in the family, mothers' age, social group and degree of crowding in the family and as far as possible, they were from the same locality of the premature.

Speirs<sup>2</sup> made an anthropometric study of prematurely born children at the age of eight years. Two hundred and seventeen prematurely born and 222 full time Glasgow children were compared.

It was found that the measurements like height, weight, bi-acromial and bi-iliac diameters were significantly greater among the full term children than among the prematurely born as is shown below.

(Mean Values)

				Male adjusted to age 5 yr. 4.6 mth.		Female adjusted to age 5 yr. 4.4 mth.	
				Premature	Mature	Premature	Mature
Weight (kg)	..	..	..	17.56	18.73	16.74	18.19
Height (cm)	..	..	..	106.22	108.00	104.69	107.32
Bi-iliac diam. (cm)	..	..	..	17.74	18.10	17.39	17.77
Bi-acromial diam. (cm)	..	..	..	23.57	24.10	23.00	23.69

The two groups were compared for overcrowding at home, sex, maternal age at the birth of the child, birth order and social class, and it was found that the two groups were almost exactly similar in these respects.

*Child Growth* : Tanner et al<sup>3</sup> made a study for predicting adult growth from infant or childhood size by longitudinal method. It was seen that the size of the new-born had little correlation with the size of the adult or even to the size of the two-year old. They suggested that prenatal environment in intrauterine life rather than heredity, determines the size of the infant. Effect of heredity is asserted later on in childhood. Correlation of childhood size to adult size rises sharply from 0.27 at birth to 0.79 at 5 years. The work was done with 42 male and 38 female children who could be followed from birth to the age of five and later on at from 25 to 30 years of age.

In many countries with well-developed health and social services it has been claimed that the present generation of children is taller and heavier compared to children 25 to 50 years ago. Keddie<sup>4</sup> reported in a paper the height and weight of school children at ages of five and 13 years in six areas of Scotland. He found that substantial gain in both height and weight for both boys and girls was observed when compared with those of school children of the same age 40 years ago. In Glasgow, the boys at the age of five were taller by 2 inches and girls by 1½ inches and heavier by 4½ and 3½ lb respectively. At 13, the boys were taller by 4 inches and heavier by 14½ lb and the girls by 3½ inches and 16½ lb. The gains were more in non-industrial areas than in the industrial areas.

*Caries of Teeth in Childhood* : As an easy preventive measure against the difficult and widely prevalent dental decay, fluorination of drinking water supply has been tried particularly in the U.S.A. The result of a ten-year study is now available, from Ast and Schlesinger<sup>5</sup>. Two comparable towns of Newburgh and Kingston had both natural fluorine content upto 0.1 ppm in their supply of drinking water. Both showed 20 decayed, missing or filled teeth per 100 teeth among 6-12 years old children. Water of Newburgh was fluorinated upto 1 ppm. During the year-to-year follow-ups, it was found that whereas the Newburgh rates for DMF were being reduced from year to year, the Kingston rates remained steady. At the end of 10 years the DMF rate for Newburgh was half of that of Kingston. Examination for the systemic effect of fluorine in children was made and it was found that none was affected but 32 Newburgh children out of 734 and none out of 940 Kingston children showed mild degree of fluorosis in teeth.

*Problem of the Handicapped Child* : A survey to find out the magnitude of the problem of the handicapped among children in Georgia (U. S. A.) was undertaken and Wishik<sup>7</sup> reported that the prevalence rate of the total types of disabilities was 108 per 1000 children under 21 years of age. A breakdown of such disabilities was as follows. Cosmetic—43, mental retardation—40, personality disturbance—29, speech defects—29, eye and visual disturbances—24, hearing defects—19, orthopaedic—17, dental—16, cardiac—10, cerebral palsy—5, epilepsy—4 and cleft palate or lip—1. For this purpose two counties with a total population of 54,291 were selected. Information was obtained from (1) voluntary notice by schools, doctors, family and others and (2) from visit by voluntary women workers to every one of 10 per cent houses. Samples of the cases found were called up and examined in a total of 24 clinics, each manned by 8 to

## Cholesteatoma

10 clinicians. Wishik found that voluntary reporting was more accurate compared to findings on home visits by women workers.

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## CHOLESTEATOMA

J. V. DeSa

Tumarkin lays the following criteria in the diagnosis of cholesteatoma:

1. Marginal perforation, 2. Hypocellular mastoid, 3. Insidious onset, 4. Characteristic odour, 5. Whitish debris, 6. Stratified squamous epithelium.

In practice the decisive criterion is usually the presence of whitish debris whereas in theory that of stratified squamous epithelium is the important criterion. While discussing various theories he observes that any theory that is acceptable should explain the insidious onset, hypocellularity of the mastoid bone and marginal perforation, which generally are present with the occurrence of cholesteatoma. In his opinion the metaplasia theory is the most acceptable one. The different pathological appearances encountered occasionally such as 'cholesterol granuloma' or 'black cholesteatoma' are merely variants or stages in a single process for which Young proposed the title 'cholesteatosis'.

Hypocellularity is explained on the fact that hypocellular mastoid in itself is the devitalized result of low grade infection in which the cuboidal epithelium undergoes metaplasia. The marginal perforation is attributed to episodes of intratympanic vacuum. Since postero-superior segment is the most vulnerable segment, there is a high incidence of perforations in this area.

*The Occurrence of Cholesteatoma in Acute Otitis:* The experimental works of Friedmann on guinea pigs revealed that a violent infection of the middle ear produces a central perforation or complete destruction of the drum and later meatal epithelium invades the tympanic cavity. Similar phenomenon is anticipated to occur in man, but Tumarkin found no case falling exactly into this category.

*The Occurrence of Cholesteatoma in Well-pneumatized Mastoid:* Simpson (1954) described 6 cases of black cholesteatoma (resulting from haemorrhage) in a series of 250 cases of mastoidectomies and in all these six cases the mastoid was cellular. Tumarkin explains this on the argument that there is a continuous gradation in the pathological response between the indolent cholesteatosis at one extreme and violent tympano-mastoiditis at the other extreme. In general the smaller the bone, the more indolent and insidious will be the pathology.

Frequent occurrence of cholesteatoma in a cellular mastoid is reported in children. In such cases the spread of the cholesteatoma is rapid and is attributed to the thin trabeculae of such bone which offer less resistance than the dense sclerotic tissue of hypocellular mastoid.

Tumarkin does not agree with Simpson who believes that cholesteatoma is not preventable. Not only the cholesteatoma but even the hypocellularity, in his opinion, is preventable if only the recurrent upper respiratory tract and viral infections of childhood are properly treated.

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**CHORIONEPIITHELIOMA—See HYDATIDIFORM MOLE**

**CIRCULATION—See HEART, PHYSIOLOGY OF**

**COLITIS, ULCERATIVE**

**Incidence:** The geographical variations in the incidence and mortality from chronic ulcerative colitis in Britain have been reported by Melrose<sup>23</sup>. He has observed that there is an ill-defined tendency for the incidence to decrease from the South to North of the country and this fact contrasts with the incidence of dysentery which is higher in the North. This would be contrary to the post-dysenteric nature of ulcerative colitis, as believed by many.

Familial incidence of ulcerative colitis and regional ileitis has been reported in 38 cases out of a total of 1204 studied by Wolarsky and Felsen<sup>12</sup>. These occurred in 21 family groups. Case histories are described and association between bacillary dysentery and ulcerative colitis is favoured.

**Psychological Aspects:** The emotional aspect and the role of other aetiological factors in relation to the patient's disease has been described by Karamchandani<sup>17</sup>. The author relates a case history from which some emphasis has been laid on the medical management of chronic ulcerative colitis in the first instance. The indications for surgical treatment in chronic ulcerative colitis have been reviewed. In another article Karush et al<sup>18,19</sup> relate their observations on psychological correlation with records of pressure changes in balloons placed in the sigmoid colon and rectum to study the activity of the colon in 6 patients with chronic ulcerative colitis. These observations are first of their kind, though are difficult to evaluate.

A follow-up study on 343 of 483 patients of ulcerative colitis was done for 10 years or until death and reported by Frank et al<sup>15</sup>. The significant observations have been tabulated in their article.

**Allergic Aspect:** The allergic aspect of chronic ulcerative colitis has been studied by Rowe and Rowe in 138 patients for 16 years and the results are impressive and prove allergy as a primary cause of this condition. In this series<sup>24</sup>, in 45 per cent of the cases, food allergy was found and the offending foods were usually milk, fruits, chocolates and condiments.

**Erythema Nodosum:** Occurrence of erythema nodosum in cases of chronic ulcerative colitis has been described by Foster and Brick<sup>14</sup> who reviewed records of 37 patients of ulcerative colitis treated between 1947 and 1953 at the Georgetown University Hospital, Washington, D. C. They found 7 cases of erythema nodosum and 3 of these had been described in detail.

An interesting observation has been made by Arnold Barger<sup>1A</sup> and others of Rochester, Minn, U.S.A. in cases of chronic ulcerative colitis. They have observed the presence of an excessive number of ganglion cells in the mesenteric plexus which does not seem to be related to the duration of the disease, the age and the sex of the patient. The possible significance of these has been discussed.

Biopsy studies in ulcerative colitis have been reported<sup>33</sup> by workers from the Radcliffe Infirmary, Oxford. These patients were getting treatment with cortisone and corticotrophin. The mucosa of the rectum and sigmoid was examined histologically by a special instrument which they have used for biopsy in two cases. Nine biopsy specimens were secured in one case and six in the other. No complications were encountered and the wound healed by the time the next biopsy specimen was taken. They found a correlation between the clinical state and the endoscopic and the histological examination. This method is recommended by them for assessing the duration of hormone treatment. Early cases of ulcerative colitis could be detected by finding inflammatory damage in apparently normal or healed mucosa. It would help in differentiating from other types of chronic diarrhoea. Prognostic help could be expected. On two occasions histological relapse preceded clinical relapse by several weeks.

**Cytological Study:** Boddington and Truelove<sup>4</sup> describe their results of smears from the rectal mucosa obtained with a special perspex device and stained by Papanicolaou method. They found abnormal epithelial cells in two-thirds of their 94 smears. These cells had large nuclei (in extreme cases they were five times the diameter of a normal epithelial cell) with chromatin pattern disturbed. These abnormal cells showed a correlation between their incidence and the severity of the disease but not with the duration of the disease. Besides having some features of malignant cells the other possibilities about their presence in rectal smears are discussed.

Motility patterns of the lower segments of ileum of two patients with ulcerative colitis and ileac stomas have been studied repeatedly for a period little over one year (Code et al, 1957)<sup>7</sup>. Two small balloons were placed in the ileum in a tandem fashion, through the abdominal stoma and connected to two glass-spoon manometers. The excursion of these were recorded photo-



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kymographically. A new type of contraction was encountered and designated "type IV". The effect of fasting, breakfast, morphine, neostigmine, atropine, methantheline, etc. has been recorded and discussed.

*Ulcerative Colitis with Pregnancy:* MacDougal<sup>20</sup> studied 64 females who had 100 pregnancies while suffering from ulcerative colitis. The period of this observation was 8 years and the cases were selected out of 244 females seen at the Gordon Hospital, London. Observations were made regarding the improvement and deterioration during pregnancy, puerperium and in successive pregnancies. The results are discussed. The deterioration in the condition of the patient has been related to local factors in the pelvic organs—hyperaemia and constipation or to psychological factors. In these patients where there was improvement, it could be explained on psychological grounds also. The feeling of satisfaction and fulfilment of successful motherhood may be a favourable stimulus with beneficial effects on colitis. It could be due to hormonal changes in pregnancy comparable to steroid therapy. It is concluded that ulcerative colitis does not impair fertility or increase the risk of abortion or still birth. In another paper<sup>10</sup> the authors have analysed the records of 110 women suffering from ulcerative colitis attending the Mount Sinai Hospital, New York. In all, 150 pregnancies occurred in these patients who were studied in four groups after the classification of Abraham et al.

Group I : Included 47 women who became pregnant when their colitis was quiescent.

„ II : Included 25 patients who became pregnant with active colitis.

„ III : Comprised of 19 women in whom the disease started during pregnancy.

„ IV : Comprised of the rest in whom the colitis started during the postpartum period.

Observations were made regarding the effect of pregnancy during the three trimesters and the postpartum period, and the incidence of abortions, still births etc. was worked out in relation to these groups. They suggest that in half of the cases there is deterioration in health in cases of colitis with pregnancy and the decision to perform therapeutic abortion must be made in the first trimester. Each patient has to be judged on her own merits. Some cases could be carried to term with corticotrophin which had no harmful effect on pregnancy. In patients with active colitis advice should be given to avoid pregnancy till the disease is quiescent. The authors advise consideration of therapeutic abortion in Group (III) patients where illness may run a severe and fatal course. The authors comment that women who had surgical treatment for ulcerative colitis went through pregnancy uneventfully.

Pregnancy in women with ileac stoma can be risky because of harmful effects (a) of pregnancy on colitis and ileac stoma, (b) of these on pregnancy, (c) of parturition on the perineum of those women who had undergone abdominoperineal resection. Scudamdre et al<sup>20</sup> describe their experience of 12 women who had a total of 18 pregnancies after ileostomy for chronic ulcerative colitis. All of them had vaginal deliveries with no maternal mortality. There were 13 live births, 4 abortions and one still birth in this series. Complications which were encountered were relapse of colitis in a rectosigmoid, bleeding from a stoma, a small crack in the skin at the edge of a stoma, prolapse of ileum through the stoma, partial obstruction of the small intestine, and painful or slow healing of episiotomy incision in case of abdominoperineal resection.

Relapse of colitis altered the course of pregnancy seriously. The authors conclude that pregnancy could be safely managed in patients with ileal stoma but should not be encouraged actively because of the possible complications related to the stoma, residual colitis or the scarred perineum. To avoid reactivation of colitis during pregnancy, resection of most or all of the colon should be done before pregnancy which would then have greater chance of success.

*Carcinoma of Colon and Chronic Ulcerative Colitis:* Thorlakson<sup>30</sup> describes 12 cases of carcinoma of the colon and rectum found during colectomy in 182 consecutive cases of ulcerative colitis, at St. Marks Hospital, London. The significant data and inferences drawn from that have been described in the paper.

An analysis of the clinical experience of the workers at Beth Israel Hospital, with ulcerative colitis during the 20 years period 1931-1950, has been described along with detailed survey of the subsequent course and late results<sup>3</sup>. Except one, all cases could be followed and the average period of observation in the living, to date, being nearly 12 years. In 245 patients, the diagnosis of non-specific ulcerative colitis was substantiated.

*Epidemiologic Data:* Nearly 47 per cent of these cases were hospitalised within the first year of their illness and in 64 per cent cases the disease was severe or serious with marked toxæmia,

haemorrhage, perforation or other grave complications at the time the patient first entered the hospital or on later readmission. There were 112 males and 133 females. Diarrhoea was the most frequent complaint and constipation, loss of weight and abdominal cramps were met with in a significant number of patients. The aetiological role of some factors has been discussed. These were respiratory infections, surgery, serious illness, bacillary dysentery and pregnancy. Sigmoidoscopy, barium enema studies and the frequency of complications and the incidence of concurrent disease were all recorded.

Analysis of the results with medical therapy indicated the greater effectiveness of antibiotics and chemotherapeutic agents as compared to simple supportive measures. Eighty-four patients required surgical treatment and in many, further colonic surgery was needed after ileostomy. Elective secondary subtotal or total colectomy carried no mortality. One-stage ileostomy and subtotal colectomy, abdominal perineal resection of the rectal stump as secondary or tertiary procedures, also carried no mortality.

The surgical mortality was highest in the first year of the disease. Fatalities occurred primarily with ileostomy, emergency secondary subtotal colectomy, unconventional operations, attempts to restore intestinal continuity and with revisions of the ileostomy for early and late sequelae. Minor and major post-operative complications were frequent after all types of surgery.

The incidence of carcinoma in this series came to 3.7 per cent. Eighty-seven pregnancies occurred in this series with 72 going to term successfully. Prognosis was favourable when the colitis was in remission.

Finally, the author's conclusions are : 20 per cent of the patients were well, 20 per cent had mild recurrence and 20 per cent experienced serious exacerbations. After surgery 17 per cent were asymptomatic, 3 per cent had a mal-functioning ileostomy and 20 per cent were dead.

Two cases of massive haemorrhage complicating acute fulminating ulcerative colitis are reported by Connoll and Carpenter<sup>9</sup> and emergency surgery was performed in these with success. The colon was markedly dilated clinically and on X-ray examination the dilated colon had come to be recognised as evidence of penetration of the ulcerative process deep into the wall of the colon. The necessity for proper surgical intervention in such cases is indicated.

In patients with ileac stomas some degree of small bowel obstruction may occur<sup>27</sup>. The causes for this are multiple, e.g. stenosis, retraction, prolapse, inflamed or tight skin-grafted stoma. Post-operative dysfunction, enteritis, peritonitis, adhesive band, volvulus, metastatic malignancy, late pregnancy, food residue etc. can cause it. In this paper the author has reported small bowel obstruction in two patients with ileac stomas, due to impaction of a plum stone in one case and a calculus in the other. He emphasizes the importance of adequate examination of the stoma for recognition of the cause of mechanical obstruction.

**Treatment.—Psychotherapy :** Pankey<sup>24</sup> describes his experiences with psychotherapy in 48 cases of ulcerative colitis at the Ipswich Hospital for six years. He gives details of striking case-histories of patients who responded and describes his views about interview with the patients. Three personality factors have been shown to be present in all cases: (i) failure to express anger, (ii) dependency, (iii) sensitivity. In the author's opinion medical management and psychotherapy should have a fair trial and surgery should be used only when these fail.

**Parenteral Trypsin :** This has been tried and reported on by a group of workers<sup>21b</sup> in seven cases of chronic colitis in which the only therapy was parenteral trypsin. In five of them the intravenous route was selected and the preparation used was Enzar while in two cases the intramuscular preparation Parenzyme was employed. Four of these patients showed clinical and endoscopic improvement with sustained remission. Side effects were encountered in all cases but no death occurred in their series. The authors suggest further evaluation of this therapy but also emphasize the possibility of complications.

**Cortisone and ACTH :** In certain articles, the authors have reported their experiences with the use of Cortisone and ACTH in cases of ulcerative colitis. In the first of these (Kirsner et al<sup>18</sup>) the authors have evaluated the place of cortisone and ACTH in the treatment of ulcerative colitis cases, of varying severity, followed up for a variable period up to three years in some cases.

The second paper<sup>11</sup> is a report of trial of ACTH in 14 cases of ulcerative colitis at Addenbrook's Hospital, Cambridge. Details of these cases are given with regard to the dosage and duration of therapy and follow-up.

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In another report<sup>32</sup> the authors report the results of their therapeutic trial of cortisone in 210 patients with acute ulcerative colitis including cases in first attack and relapse. They obtained results which were significantly better in the cortisone-treated groups (109 patients) than in the controls (101 patients) at all levels of severity and in both the first attack and the relapse. To assess the results the following factors were taken into account: weight, temperature, number of stools, erythrocyte sedimentation rate and haemoglobin level. There were fewer deaths in cortisone-treated groups as compared with the controls, but pyogenic complications were rather more frequent. They conclude that prompt treatment with cortisone during a first attack of ulcerative colitis offered a good prospect of cure.

Another report<sup>21</sup> from the Toronto General Hospital, St. Michael's and the Sunny Brooks Hospitals, deals with results obtained with ACTH and cortisone in 109 cases of idiopathic ulcerative colitis seen between 1950 and 1955. These have been compared with the results obtained in 250 cases seen between 1930 and 1950, treated by other means.

*Adverse Effects:* Brooke<sup>5</sup> reports his observations in 3 cases of ulcerative colitis who came for operation after treatment had been tried with steroids for a period of 4, 5 and 6 weeks respectively without response. There was active disintegration and gross friability of the wall of the colon leading to fatal peritonitis. The author states that disintegration and adhesions were observed in only the cortisone-treated patients.

*Local Hydrocortisone:* The use of local hydrocortisone in cases of ulcerative colitis has been reported by workers from the Radcliffe Infirmary, Oxford<sup>31</sup>. The steroid (60-120 mg) was given by a slow intrarectal drip in saline alcohol, for a variable period of 2 to 3 weeks. Patients with secondary infection were excluded. Sigmoidoscopy and biopsy were done frequently and the patients were followed up for one year. The details of the results are given in the original paper which may be referred to. The clinical impression from this trial is that the patients experience symptomatic relief but the authors admit the possibility of psychosomatic effect as this was not a controlled trial.

*Surgery in Ulcerative Colitis:* Levy et al<sup>19</sup> have described their observations in five patients of severe chronic ulcerative colitis with obsessive-compulsive behaviour. These patients were studied before and after prefrontal lobotomy at the University Hospital, Oklahoma. Mental symptoms responded very satisfactorily in all cases.

Aylett<sup>2</sup> describes surgical modifications in the technique of ileorectal anastomosis in 23 cases of ulcerative colitis. The records of these patients and their progress have been described. The majority of the patients were operated upon in one stage, some were actually ill and in a fulminating phase of the disease.

A review<sup>6</sup> of the results of surgery and follow-up in 131 cases of ulcerative colitis has been described. Two hundred and twenty-one operations were performed and the post-operative observations and the place of surgery in this condition have been mentioned. In the author's experience impotence in men was not a problem.

A modification of the conventional technique of ileostomy has been described by Goligher<sup>16</sup> and the incidence of ileostomy dysfunction is said to be much less with this.

*Follow up:* A valuable description<sup>1b</sup> of the problem created by the ileal stomas is described in 70 male and 54 female patients of chronic ulcerative colitis followed up for a long period. The original paper should be consulted for detail.

Another report from the Mayo Clinic describes a study in 45 patients of ulcerative colitis who were subjected to subtotal colectomy<sup>8</sup>. The plan of surgical technique later and the post-operative follow-up has been described. The authors have drawn no definite conclusions from this study but advise that if ileorectal anastomosis is not possible at the time of colectomy, as much of the rectum as possible should be removed at the initial operation and the rest later. The hazard of malignancy is real and the continuation of the disease with its associated discomforts frequently requires later resection.

A study on the incidence, development and management of the various anorectal complications has been reported in 200 consecutive cases of chronic ulcerative colitis. For details the original paper<sup>25</sup> should be consulted.

*Roentgen Observations:* In 13 patients of idiopathic ulcerative colitis, the post-operative ileal function was studied by barium enema,<sup>13</sup> through ileostomy stoma and by oral passage of

barium-water suspension. Ileostomy had been done in these patients for 6 months or longer for severe idiopathic ulcerative colitis. The subjects selected were those restored to normal body weight, free from evidence of partial obstruction with normal volume, consistency and odour of ileal discharge. In 3 of these patients, the workers could show that the lower ileum is capable of inspissating its content irrespective of the presence or absence of colon.

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**COLON, POLYPOSIS AND ADENOCARCINOMA—RELATIONSHIP  
TO SCHISTOSOMIASIS**

*V. C. Anguli*

Two hundred and thirty seven polyps of the large intestine were studied for malignant changes and schistosomal infection. Of the total, 225 were associated with schistosomiasis.

Although inflammatory and epithelial changes were observed in more than 45 per cent of the polypoid tumours associated with schistosomiasis, no relationship to malignancy could be established.

Seventeen of 98 carcinomas of the large intestine were associated with schistosomiasis. Detailed histologic studies revealed no outstanding features to distinguish parasitic from non-parasitic groups.

Although schistosomiasis is believed to be responsible for benign polypoid tumours of the large intestine it is concluded that both schistosomiasis and schistosomal polyps of the large intestine bear no proved histologic relationship to carcinoma.

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**COMA IN HYPOPHYSECTOMY—See PITUITARY GLAND**

**CONGENITAL MEGACOLON—See HIRSCHSPRUNG'S DISEASE**

**CORNEAL GRAFTING**

*T. B. Gupta*

*History* : The history of transplantation of cornea extends over 100 years. It may be traced as far back as 1797 when Erasmus Darwin wrote as follows : " After ulcers of the cornea, which have been large, the inequalities and the opacities of the cornea obscure the sight : in this case could not a small piece of the cornea be cut out by a kind of trephine about the size of thick bristle, or a small crow-quill, and would it not heal with a transparent scar ? " It would appear from these restless thoughts that blindness due to corneal ulceration was an urgent social problem in those early days. The treatment of this malady (corneal scars) by the transplantation of tissue had two phases. For most of the 19th century, heteroplasty was in vogue. However it was soon realized, largely due to efforts of Power and von Hippel, that homoplasty was essential for achieving success. By the beginning of this century, interest in the transplantation of the cornea had died out. Thanks to Zinn, it was revived in 1905. He successfully carried homoplastic transplantation of the cornea, and Elschmig elaborated his method. At the beginning of the first World War, Elschmig became the protagonist of the full-thickness graft from a human donor and the publications of his school extended to 1930. The greatest stimulus to modern keratoplasty in recent years, however, has come from the happy combination of the French surgeons Pautique, Sourdille, and Offret, with their Swiss colleagues, Franceschetti and others, which resulted in the brilliant publication of " Less graffes de la cornée " in 1948. Nor must be forgotten the valuable contributions of Filatov, Castroviejo, Barraquer, Arruga, Amsler, Streiff, Rougier and Babel.

*Indications* : Although initially conceived for treating corneal opacities, keratoplasty is today employed as an accepted method of treatment for various other conditions which are as follows :

*Optical* : For the improvement of vision in the case of corneal affections.

*Therapeutic* : For stopping an evolutionary process of the cornea or in other instances stimulating the clarification of a scar.

*Cosmetic* : This is applied in cases of white, apparent leucomas in blind eyes and in which the cosmetic result is better than by tattooing with ink or platinum chloride.

Broadly speaking, optical keratoplasty is indicated when visual acuity is less than 6/60, owing to corneal nebulæ, the degree of which is either stationary or progressive as in the case of degenerations. Since the visual result of operation may not be better than before operation in some cases at least, corneal grafting should not be resorted to where visual acuity is more than 6/60. The various corneal affections susceptible to keratoplasty are as follows :

1. *Keratoconus* : It offers the best prognosis. Corneal transplant in this disease is decided upon when vision is not adequately improved by contact lens or the growth of the cornea is alarming. In such cases, perforating graft is indicated.

2. *Corneal Dystrophies* : The granular type and lattice-like type, in the dominant group, are of excellent prognosis. The lamellar technique is employed as the opacities are most frequently superficial. If the opacities are situated more deeply in the corneal substance, a perforating technique will give good results. Both these affections constitute the ideal indications for keratoplasty, the absence of blood vessels in them being total. The macular type, a recessive form is best treated by a perforating graft as the opacities are deep in the parenchyma.

3. *Previous Keratitis in Childhood* : The primary factor is the vascularisation of the lesions rather than their extent or their aetiology. The choice of the graft would be influenced nevertheless, both by the vascularisation and extent of the lesion. Because of the age of the lesions and the very slight possibility of a post-operative flare-up, the prognosis is usually favourable. Cases of parenchymatous keratitis present a difficult problem. Frequently in the vascular form, vision may be sufficient to rule out an intervention, except if the good condition of the fellow eye and the professional requirements of the patient allow us to surpass the upper limit of vision. The prognosis remains doubtful on account of the deep vascularisation which traverses the cornea, and the marked tendency to flare-up. In the avascular form also the prognosis is not as good as might be expected. Leucoma following ophthalmia neonatorum is also of doubtful prognosis on account of its frequent adherent nature, the associated nystagmus and amblyopia.

4. *Keratitis in Adults* : Corneal opacities due to herpes and rosacea are amongst the most favourable cases. All leucomas regardless of their nature, are operable. If the conditions are unfavourable *a priori* and cannot be corrected at one sitting, several operations may have to be done. In trachoma the prognosis is doubtful on account of the extreme surface vascularisation which shows a marked post-operative tendency to exacerbation. The chances of a favourable outcome are diminished because not only the cornea but also the conjunctiva and tarsus are attacked by the disease. In the case of a cataract with a dense corneal nebula, it is preferable to do a keratoplasty first and an intra-capsular extraction later. A corneal graft in aphakia is difficult and prognosis is doubtful. In such cases, lamellar graft is recommended. In case one is compelled to employ penetrating technique, the injection of air at the end of the operation is of primary importance.

There are certain conditions which are regarded as contra-indications to corneal grafting in the sense that failures are cent per cent. These conditions are as follows :

1. Neuroparalytic keratitis—The graft does not take in a cornea deprived of its neurotrophic system.
2. Leprous keratitis—The graft succumbs to the original disease.
3. Corneal lesions in pemphigus—The absence of lacrymal secretion and the associated mucosal lesions condemn the graft to certain opacification, more often to necrosis.
4. Lesions in erythema exudativum multiforme—These lesions (Stevens-Johnson's disease) constitute a contra-indication even though there is some chance of survival of lamellar graft with temporary useful visual acuity.
5. Traumatic conditions—Leucomas resulting from explosions and burns by caustic substances or melting metals are among the least favourable conditions for operation.

Therapeutic grafts comprise grafts having the common characteristic of being executed during the evolutionary period of a corneal affection, whether this be of an irritating, inflammatory or degenerative nature. Their objective is to stop the evolution of acute, torpid, or relapsing lesions and to exert a trophic action on the cornea surrounding the graft. They are particularly useful in the following cases :

1. Herpetic and disciform keratitis—The slow evolution of these conditions often resulting in opacification of the cornea is quickly cut short by superficial graft.
2. Torpid corneal ulcers—The different varieties are for all intents and purposes excised and cured by the lamellar graft.
3. Intra-corneal abscess—These cases benefit most by therapeutic grafts. It is well known that all other forms of treatment fail and end in blindness.
4. Acute interstitial keratitis—Therapeutic graft as compared to cortisone treatment is certainly the better safeguard against relapses.
5. Recurrent pterygium—The evolution of a pterygium is most favourably influenced by therapeutic lamellar graft placed at the limbus.

## Corneal Grafting

6. Corneo-scleral tumour—In such cases lamellar excision is possible and the defect so created can be replaced by a graft of same form.

*Varieties of Keratoplasty* : There are four types of corneal transplantations :

1. Total penetrating keratoplasty, in which the whole cornea is removed and the defect is replaced by whole cornea from the donor. This has proved on the whole very unsatisfactory due to supervention of glaucoma in most cases.
2. Total non-penetrating (lamellar) transplant is rarely used as the results are reported to be always disappointing.
3. Partial lamellar corneal transplantation is suitable for cases where the opacity is situated only in the superficial layers of the cornea. It is a comparatively easier operation. I have personal experience of this type of keratoplasty and the results in suitable cases have been gratifying. In cases which fail to succeed no harm is done to the patient and the vision is not worse than before.
4. Partial penetrating grafting is the method employed in the majority of patients.

*Donor Material* : It can be obtained both from patients and the cadaver. Age of the donor is immaterial. The donor material is preserved in most of the eye banks which I happened to visit during my European tour in 1956, by immersion of the excised eye in a sterile glass container of hour-glass shape, filled with sterile liquid paraffin. The cornea is kept pointing downwards to occupy the narrow waist of the container, and is bathed in paraffin. This container is closed by glass stopper and is kept in a refrigerator in which the temperature is maintained at 4°C. Animal experiments have been carried out to find a technique of freezing excised corneas by immersion either in liquid hydrogen at minus 195°C, or isopentane at minus 159°C. The cornea is placed in a vial, and a vacuum pump extracts the moisture ; the vial is then sealed. Re-hydration of the cornea is effected by breaking the tip of the vial and immersing it in either saline, serum or aqueous. It is desirable to take cadaver donor material within 2 hours of death, for after this time, post-mortem cultures taken from structures which form the anterior segment of the eye are frequently positive for staphylococci, streptococcus proteus and bacillus subtilis. For this reason, it is always advisable to irrigate the graft with a solution of penicillin and streptomycin before placing it in the eye of the recipient.

There has been no modification recently in the technique of grafting and therefore no mention is made in this article regarding this. Observations regarding the complications during the operation and after have received intensive study and comments. Complications during the operation of a penetrating keratoplasty are, unforeseen anterior synechiae, collapse of the eye, injury to the iris and the lens, extrusion of the lens and vitreous loss. Post-operative complications have been displacement of the graft, delay in the formation of the anterior chamber, iris prolapse, anterior synechiae, glaucoma, descemetocoele and opacification of the graft. The graft may become opaque because of previously existing vascularisation, symblepharon, etc. Therefore, the eye could be rendered more favourable by preliminary surgery, before keratoplasty is attempted. In order to prevent injury to the iris or lens with trephine or knife, the instrument should be withdrawn from the cornea the moment the anterior chamber has been entered. Also to prevent injury to intra-ocular structures, manipulations within the eye must be carried out with scissors having blunt points and with toothless forceps.

In performing keratoplasty with large grafts, the lens may extrude. Adequate paralysis of the orbicularis, use of speculum or retractor which does not press against the eye ball, the addition of hyaluronidase to the retrobulbar injection to reduce the tension of the eye and pressure upon the eye before starting the operation tend to prevent these complications. The incidence of extrusion or protrusion of the graft, development of fistula, hernia of the iris and anterior synechiae are said to be greatly reduced if good apposition of the borders of the graft and cornea of the host is secured by direct suturing.

High astigmatism is usually observed in keratoconus when the graft has not been large enough to remove the whole deformity. Therefore, in keratoconus, the graft should be large enough to replace the whole cone to obtain a better curvature. If post-operatively the transplant has a tendency to protrude, irregular healing will take place with the development of high errors of refraction. This protrusion has been treated by the application of a pressure dressing from the third post-operative week until adequate curvature has been obtained.

Fuchs epithelial dystrophy often recurs over the graft unless the operation is performed at an early stage of the disease (Castroviejo), post-operative vascularisation of the graft is handled by

## Coronary Heart Disease, Incidence in India

the administration of cortisone locally and if necessary systemically. If these fail, beta irradiation has been recommended. All foci of infection should be eradicated, as according to some authorities they might be responsible for the late opacification of the graft.

**Keratectomy** : During recent years this operation has come into vogue. It consists in excising some portion of the anterior layers of the cornea in cases where the pathology is limited to these layers. This operation often gives fair amount of visual improvement and can be undertaken in the absence of donor material and also in cases which are considered to be unsuitable for keratoplasty because of vascularisation etc. Castroviejo has given detailed indications and technique of doing this operation and readers are referred to his writings for the same.

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## CORONARY HEART DISEASE, INCIDENCE IN INDIA

O. T. Samani

Last 30 years or so have seen an increasing interest all over the world in the incidence of coronary heart disease.

Earlier surveys in the Western countries laid down its incidence as 10 per cent in England (Coombs, 1926)<sup>2</sup>, 37 per cent in Massachusetts, U.S.A. (White and Jones, 1928)<sup>10</sup>, 19.1 per cent in England (Perry, 1934)<sup>6</sup>, 2.5 per cent in Ceylon (Gunewardene, 1935)<sup>3</sup>, 17.6 per cent in Mexico (Chavez, 1942)<sup>1</sup>. Recent surveys by White (1951)<sup>11</sup> in Massachusetts showed the incidence as 48.5 per cent.

No authentic surveys of the incidence of coronary disease in India have been available prior to about a decade. Sanjivi<sup>8</sup> from his study of 616 cases of cardiovascular disease from South India (Madras State) in 1946 reported the incidence of coronary heart disease as 13 per cent. Devichand<sup>3</sup> from Northern India (the Punjab) reported in 1946 the incidence ("Hypertension and Coronary Heart Disease Group") as 25 per cent. Vakil<sup>9</sup> from Western India (Bombay, 1949), from his survey of 1,860 cases of cardiovascular disease reported the incidence of coronary heart disease as 13.5 per cent. Malhotra<sup>5</sup> from the Punjab (1951) gives the figure for this disease as 23.4 per cent from his study of 692 heart cases and 48.8 per cent in a group, "hypertension coronary group."

Coronary heart disease in low income population on the West Coast of India (Bombay State) was reported by Samani<sup>7</sup> and his observations were as follows. A total number of 37,896 medical admissions at the Sir J. J. Hospital, Bombay, were surveyed. Of these, 2,081 cases were of organic heart disease. Of these 2,081 cases, 252 (12.1 per cent) were of coronary heart disease. Thus, this condition formed 12.1 per cent of all cases of organic heart diseases and 0.66 per cent of the total medical admissions. Other arteriosclerotic heart diseases (on the basis of W. H. O. International classification) formed 3.4 per cent and were excluded from this series.

According to the clinical types, these 252 coronary heart disease cases were distributed as follows (Samani, 1956) :

Type	No. of cases	Percentage
Myocardial infarction .. .. .	208	82.5
Myocardial ischaemia .. .. .	38	12.3
Coronary insufficiency and others .. .. .	6	2.3

Sex distribution of these 252 coronary heart disease cases in this series was as follows :

	No. of cases	Percentage
Males .. .. .	230	91.3
Females .. .. .	22	8.7



## Coronary Heart Disease, Incidence in India

In any of the above three clinical types, male cases were about 5 times as many as females. The male to female ratio was higher in the younger age groups.

All workers on the subject agree that no age is exempt from coronary *artery* disease while the incidence of coronary *heart* disease varies from young to old age but increases with increase in age.

The peak period for clinical manifestation of the disease in the Western countries is observed in the age group 50 to 60 years. In our country, from studies available, it appears to be a decade earlier—at any rate in the Western part of India. Vakil (1949) reported 250 cases of coronary heart disease and observed that the peak period was in the age group 40-49 years. In Malhotra's series of 200 coronary heart cases from Northern India, the peak period was in the age group 50-59 years—i.e. a decade later than that observed by Vakil and Samani in Western India.

Regarding age distribution in Samani's series of 252 cases (1956), the following observations were made :

1. No case below the age of 10 years was observed.
2. With the increase in age, there was a higher incidence.
3. The maximum incidence was in the age group of 41-50 years, a decade earlier than in the Western countries and than that mentioned from the Punjab. Whether coronary heart disease manifests a decade earlier in Bombay State compared to the Western countries and the Punjab state, whether the difference is real—based on a difference in the aetiological factors, or whether it is more apparent than real due to other factors like selection of clinical material and consequent probable statistical illusion, one cannot dogmatically opine unless similar comparable surveys from other states are available or freshly undertaken, laying emphasis on various aetiological factors responsible for this disease.
4. Out of 252 cases, there were 65 cases (25.7 per cent) below the age of 40 years. Of these the maximum number (41 cases or 16.3 per cent) was in the age group 31-40 years.

Peak period (41-50 years) observed in overall group of coronary heart disease was also observed for (1) Myocardial infarction—70 cases (32.8 per cent), (2) Myocardial ischaemia—14 cases (36.8 per cent).

*Coronary Heart Disease in Different Communities* : Question of "communities" or "castes" in India is on a different footing to "races" in Western countries. Western surveys are based on races. Communities or castes in India are based mainly on religion and hence the difference really boils down to different dietetic habits, namely, vegetarian or non-vegetarian. The main communities in India are Hindus, Muslims, Christians, Parsis and others. Hindus who form the major community in our country are mostly vegetarians. Dietetic habits amongst Hindus of comparable economic status themselves also vary in different parts of the country. When the economic factors are added, there remains nothing like choice in diet. There can therefore be no comparable figures to the West. Large scale surveys on these lines for this disease are not available from different parts of our own country also.

Out of 252 cases of coronary heart disease (all groups) 117 cases (46.4 per cent) were Muslims, 82 (32.5 per cent) Hindus, 7 (2.6 per cent) Parsis, 38 (15 per cent) Christians and 8 (4.5 per cent) others. Muslims form the majority because the hospital is so located that the majority attending this hospital are Muslims.

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**CORONARY HEART DISEASE, MORTALITY RATE IN INDIA**

O. T. Samani

Vakil<sup>2</sup> (1949) in his series of 250 cases of coronary heart disease reported mortality rate as 29.2 per cent. For males it was 27.7 per cent and for females 42.3 per cent. For different age groups it was higher in the 'old age' groups. It also showed a consistently higher rate in females in all age groups. Immediate mortality in a series of 115 cases (Vakil, 1949) of coronary occlusion, was 33.9 per cent. Below 40 years the mortality rate was 26.3 per cent. It was 45.5 per cent in females and 32.7 per cent in males.

In the author's series<sup>1</sup> (Samani, 1956) of 252 cases of coronary heart disease there were 95 (37.7 per cent) deaths. Of these 83 (36 per cent) were males and 12 (54.5 per cent) females. Age group 41-50 (peak period group) showed 24 (46.5 per cent) deaths out of 86 admitted in this age period. It was also observed that although the incidence was higher in males, mortality rate was higher in females. There is a steady fall in the mortality rates in males, through age decades until the age of 55 after which they show a rise again. There was no such consistency in females. Death rate for "peak period" group (41-50 years) was 27.8 per cent for males and 28.5 per cent for females. It is also pointed out that prognosis in the peak period group is better than in the other age groups. Individually all decades show constant preponderance of male deaths over female deaths although the number of deaths in relation to the number admitted (i.e. percentage mortality) is higher in females than in males. This is because the absolute number of males treated is more than females.

The mortality rate in young adults with coronary heart disease below the age of 40 years, was 56.2 per cent. In the case of myocardial infarction it was 60.3 per cent. Death rate in Hindus in the author's series was 37.8 per cent, Muslims 40.1 per cent, Parsis 42.8 per cent. Thus the trend in the present series pointed to a poorer prognosis in the minor communities (? due to dietetic differences). The same observation held good for individual clinical types of coronary heart disease.

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**CORONARY HEART DISEASE, TREATMENT OF**

J. C. Banerjee

Coronary heart disease, which is occurring with increasing frequency, presents three distinct types of symptom-complexes: (1) angina pectoris, (2) coronary insufficiency, and (3) myocardial infarction. In any discussion of the management, these conditions require to be considered separately.

**Angina Pectoris.**—The object in its management is two-fold : (1) to relieve the attack and (2) to prevent future attacks. Recent studies have not shown any factor better than the avoidance of an amount of exertion likely to cause the pain and sublingual use of 1/200-1/100 gr of nitroglycerine during the attack or even for its prevention. It has been shown to correct the ischaemic S-T depression in the E. C. G., after a standard exercise (Russek, 1955)<sup>1</sup> provided the tablets are not too old in which case they lose the potency ; a preparation like Angised (B. W. and Co.) overcomes this drawback.

Nitroglycerine is a short-acting coronary dilator, the action lasting for 15-30 minutes. Many long-acting coronary vasodilators are available in the market but very few of them have proved to be effective. Russek et al (1955)<sup>2</sup> have compared the action of a number of such drugs regarding their effect on the S-T segment depression in the E. C. G. during a standard exercise test (Master's two-step test) in patients with coronary heart disease. Their results have demonstrated that penta-erythritol tetranitrate in doses of 10 mg taken on an empty stomach and at least an hour before the meals, has a vasodilator action of about 5 hours, similar to that of nitroglycerine for a short period. Papaverine in large doses has a similarly prolonged effect. Paveril (Lilly), a synthetic analogue of papaverine has a much weaker action. Other drugs like aminophylline, Roniacol (Roche), Khellin, priscoline, heparin and dicoumarol and whisky had little or no effect on the E. C. G., response to exercise test. Further studies by the same authors show that Metamine (triethanolamine trinitrate biphosphate) used in 4 mg doses 4 times a day produces no significant change in the E. C. G., after exercise. Fuller and Kassel (1955)<sup>3</sup> hold the same view. Nitroglyn (sugar-coated granules of nitroglycerine for sustained effect) used in a dose of 4/25 grain, has slight to moderate effect on the E. C. G. after exercise (Russek et al, 1955). In no

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instance the sustained-action preparations have proved superior to pentaerythritol tetranitrate in producing a normal exercise response. The latter is the only drug, in their opinion, worthy of the designation of a "long-acting coronary vaso-dilator." Nitroglycerine ointment has recently been advocated for application to the chest, initially to the extent of 1 in. from the tube and gradually increasing to 2½ in. of the ointment every 4 hours during the day for prolonged effect (Hefner et al, 1957)<sup>5</sup>.

Choline theophyllinate in oral doses of 200-500 mg thrice daily causes definite clinical improvement in 52.3 per cent of cases after 2-4 weeks (Aravanis and Luisada, 1956)<sup>6</sup>.

Vitamin E (alpha tocopherol) has been used for a long time but has not proved to be useful in angina pectoris (Rinzler et al, 1950)<sup>7</sup>.

Anti-thyroid drugs like thiouracil derivatives have been recommended for reducing the metabolic activity and consequently the demand for an increased coronary blood flow (Raab, 1945 ; Waitzkin, 1951)<sup>8,9</sup>. Treatment under close supervision for a long time is necessary and the results are not very encouraging.

Blumgart et al (1955)<sup>10</sup> have reported marked improvement in half and good results in the remaining half of their patients of angina pectoris, successfully treated by radioactive iodine. 75 per cent of cases in their series showed worthwhile improvement.

Jaffe et al (1955)<sup>11</sup> have observed excellent results in 56 per cent and good results in 37 per cent of 94 patients with anginal attacks under radioactive iodine therapy. Radioactive iodine is indicated in patients with severe angina where other medical measures have failed. It should not be used in cases of angina pectoris of recent origin.

Surgical procedures e.g., paravertebral injection of alcohol or procaine to block painful impulses from the heart (White and Bland, 1948)<sup>12</sup>, revascularisation of the pericardial surface to open out fresh collateral channels (Mason, 1951)<sup>13</sup>, poudrage, i.e., cardiopericardioplexy (Thompson et al, 1953)<sup>14</sup>, de-epicardialisation by application of phenol to the pericardium (Harken et al, 1955)<sup>15</sup>—all have limited value in the small group of cases of severe angina pectoris, refractory to other methods of treatment. There is no convincing evidence that these operations are of any value, in view of the already existing intercoronary anastomoses in patients with severe angina pectoris and coronary occlusion (Blumgart et al, 1950)<sup>16</sup>.

**Coronary Insufficiency.**—There are cases of angina pectoris where pain occurs more frequently, is not related to the degree of exertion, does not disappear promptly on cessation of effort or after sublingual use of nitroglycerine. On the other hand, pain comes on at night even in the recumbent posture (angina of decubitus), increases in severity, lasts for more than 15 minutes or more and fails to respond to nitroglycerine. This condition is called acute coronary insufficiency. Scherf and Golbey (1954)<sup>17</sup> advocate not to make use of this term as they do not recognise it as a disease entity. There may be a number of causes underlying this altered clinical picture such as a premonitory stage of small or large myocardial infarctions, paroxysmal tachycardia, internal haemorrhage, and paroxysms of hypertension associated with phaeochromocytoma. Bed rest for a period of at least 3 weeks, anticoagulant therapy and treatment of the aetiological factor are essential. Bed rest will prevent the development of myocardial infarction and promote collateral circulation. Anticoagulant therapy is calculated to avert impending myocardial infarction. It should be continued for a period of at least 3 weeks after complete subsidence of pain.

Of 25 cases of acute coronary insufficiency, not treated with anticoagulants, no less than 12 developed acute cardiac infarction within 3 weeks, 5 of whom died ; of 33 cases of acute coronary insufficiency treated with anticoagulants only 2 developed cardiac infarction within three months and neither of them died while another patient died suddenly a week after the onset of treatment (Wood, 1948)<sup>18</sup>. On the contrary, Schlachman (1957)<sup>19</sup> has recently reported the failure of anticoagulant therapy to prevent myocardial infarction in patients with premonitory symptoms of an impending coronary occlusion. On the other hand, Engelberg et al (1956)<sup>20</sup> selected 200 cases who had an attack of myocardial infarction at least 3 months ago and divided them into 2 groups, one group receiving 200 mg of heparin (conc. aqueous solution) subcutaneously, twice a week, while the other receiving isotonic saline injection in a similar manner. Within a period of 2 years there were 18 non-fatal recurrences and 21 deaths from cardiovascular disease in the control group and 5 non-fatal recurrences with 4 deaths from heart disease in the heparin-treated group.

**Myocardial Infarction.**—*Bed rest* : Immediate bed rest is essential to prevent thrombo-embolism, congestive cardiac failure, shock, arrhythmias, cardiac rupture and sudden death.

Patients with dizziness or fainting feeling due to hypotension should be made to lie flat in the bed whereas those with clinical signs of congestive cardiac failure should be propped up.

After a minimum period of 3 weeks of bed rest, if the sedimentation rate has returned to normal, the electrocardiogram shows a small infarct and if there are no complications, the patient may be allowed resting on a couch for a further fortnight. Six weeks' to 3 months' convalescence is usually needed after which the patient gradually resumes his normal activities. If there are complications and the size of the myocardial infarct is large the period of bed rest should be increased accordingly.

**Relief of Pain** : Morphine sulphate  $\frac{1}{4}$  gr should be given intramuscularly at half hour intervals till the pain is relieved, the total dose not exceeding 1 gr in 24 hours. If it is severe  $\frac{1}{2}$  gr may be given immediately by the same route. If the pain is very excruciating and there is evidence of collapse a slow intravenous injection of  $\frac{1}{4}$  gr of morphine dissolved in at least 2 c.cm of distilled water or saline solution is advisable (Blumgart, 1955 ; Wood 1956)<sup>21, 22</sup>. In cases with known morphine intolerance, administration of pethidine and methadone has to be considered.

**Oxygen Inhalation** : It may be given in severe cases or in those with cyanosis, severe pain, and dyspnoea ; pain and the heart rate are favourably influenced (Blumgart 1955)<sup>23</sup>. Oxygen helps to ensure saturation of the arterial blood passing through the lungs, particularly when respiration is depressed due to morphine or otherwise.

**Shock** : The treatment of shock should be commenced as early as possible. Shock is to be combated with vaso-pressor drugs. Noradrenaline 10 mg, dissolved in a litre of 5 per cent glucose solution may be given by intravenous drip at the rate of 10-20 drops per minute, so as to regulate the maintenance of blood pressure at about 120 mm Hg ; it should be continued as long as necessary upto a maximum period of 72 hours (Shirley Smith and Guz, 1953)<sup>24</sup>. If this treatment is adopted within three hours of the onset of shock, the death rate is only 13 per cent (Griffiths et al, 1954)<sup>25</sup>.

**Anticoagulant Therapy** : Lot of work has been carried out as to the suitability of anticoagulant therapy in myocardial infarction. Irving S. Wright (1957)<sup>26</sup> found no difference between anticoagulant-treated and anticoagulant-untreated patients in the number of new infarcts or extensions at autopsy, although the thromboembolic complications were reduced from 43.7 per cent to 27.5 per cent after treatment with anticoagulants. All cases of myocardial infarction do not necessarily require anticoagulant therapy. Russek and Zohman (1957)<sup>27</sup> classified cases of myocardial infarction into good-risk cases and poor-risk cases at the time of the first examination. Good-risk cases are those who never had previous infarction, intractable pain, persistent shock, significant cardiac enlargement, gallop rhythm, congestive heart failure, auricular fibrillation or flutter, intraventricular block, diabetic acidosis and other states predisposing to thrombosis and such cases do not require anticoagulant therapy. The poor-risk cases should however be treated with anticoagulants. Before selecting cases for anticoagulant therapy, history of any disease capable of producing easy bleeding e.g. acute peptic ulcer, haemorrhagic blood dyscrasias, malignant hypertension, history of recent surgery on the nervous system and history of surgery that left wide oozing surfaces e.g. prostatectomy, should all be taken into consideration. With careful clinical supervision and reliable laboratory support, any serious bleeding is seldom encountered.

Heparin in a dose of 15,000 units should be given intravenously at the commencement and thereafter, intramuscularly in the same dose at 8 hourly intervals for the first two days. Dindevan or Tromexan should be given concurrently. Dindevan should be administered in doses of 150 mg on the first day, 100 mg on the second day and 50 mg on the third day and Tromexan may be administered in doses of 900 mg on the 1st day, 600 mg on the second day and 300 mg on the third day. Subsequent administration of these drugs should be regulated according to the prothrombin time which should be maintained at two and a half times the prothrombin time of a normal control. If the prothrombin time reaches 60 sec. or more without bleeding, 10 mg of vit. K<sub>1</sub> in tablet or liquid form is to be administered orally with orange juice. If there is gross bleeding or if the prothrombin time is above 80 sec., 20 mg of vit. K<sub>1</sub> should be

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given intravenously or orally at once and should be repeated if the prothrombin time does not drop within 3 to 6 hours (Russek and Zohman, 1954)<sup>28</sup>.

Anticoagulant therapy should be usually carried out for 21 to 28 days (Blumgart, 1955)<sup>29</sup>. The work of Nichol and Borg (1950)<sup>30</sup>, regarding the institution of permanent anticoagulant treatment to prevent further attacks of coronary thrombosis is under trial and reports from Suzman et al (1955)<sup>31</sup> with regard to long-term anticoagulant therapy for several years in such cases appear to be promising.

**Cortisone** : Johnson et al (1953)<sup>32</sup> reported on the reduction in the size of experimentally produced myocardial infarct but subsequent work of Opdyke (1953)<sup>33</sup> and Hepper et al (1955)<sup>34</sup> has not confirmed it.

**Atropine Sulphate** : Atropine sulphate 1/100 gr hypodermically every 8 hours during the first 3 or 4 days may block adverse reflexes which occur after myocardial infarction (Blumgart, 1955).

**Congestive Cardiac Failure** : It should be treated promptly with appropriate posture, a low sodium diet, mercurial diuretics, and digitalis. Digitalis should not be withheld when congestive cardiac failure has set in, for the fear of precipitating ventricular tachycardia and fibrillation (Gilson et al, 1950<sup>36</sup> ; Boyer, 1955)<sup>37</sup>.

**Disturbances of Rhythm** : Drugs like quinidine, procaine amide, digitalis or ephedrine should be used whenever necessary and may be life-saving measures.

**Diet** : For the first few days semi-starvation with a diet of 800 calories has been found to reduce the mortality rate by half (Master et al, 1936)<sup>38</sup>. For the first 48 hours fruit drinks, soft or stewed fresh fruit, sugar and a little milk should be given. Later, the diet should be light, of low caloric value, less bulky and contain little fat. Sodium is to be restricted in presence of congestive cardiac failure. Fluids sufficient to produce a daily urinary output of 1500 cc. may be given (Blumgart, 1955)<sup>39</sup>.

**Preventive Aspect of Coronary Heart Disease.**—Coronary heart disease is mainly due to coronary atherosclerosis, which is associated with an abnormal lipid pattern in the blood. Keys (1952)<sup>40</sup> has emphasized on the use of diets with low total fat and total caloric intake to prevent overweight. Low fat diet continued for prolonged periods reduces the concentration of abnormal serum lipids (Gofman et al, 1950, 1953)<sup>41</sup>. Best et al (1954)<sup>42</sup>, Barber et al (1955)<sup>43</sup> report a decrease in total serum cholesterol with reduction in cholesterol-phospholipid ratio on daily administration of sitosterol in divided doses before each meal which interferes with the absorption of cholesterol from the alimentary tract. Reduction of serum lipids has followed the use of diet containing vegetable fat and no animal fat (Barr, 1955)<sup>44</sup>. The administration of potassium iodide and thyroid hormone may decrease the permeability of the vascular endothelium and thus protect against the development of atheromatous lesions (Katz et al 1953)<sup>45</sup>. The filtration of blood lipoproteins through the intima of blood vessels is favoured by high filtration pressure which is present in hypertension. Control of hypertension is therefore likely to check the progress of atherosclerosis (Page, 1954)<sup>46</sup>. The use of oestrogens may modify the serum cholesterol level and abnormal lipid pattern (Steiner et al, 1955)<sup>47</sup> but the prevention of development of atheromatous lesions has not yet been demonstrated.

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**CORTISONE**—See HORMONES, STEROID

### **CORTISONE AND CORTICOTROPHIN IN THE REACTIVE EPISODES OF LEPROSY**

R. Subramaniam

Erythema nodosum leprosum occurs as an acute, subacute, or chronic reaction characterised by the occurrence of erythematous nodules from the extensor surfaces of the extremities, the face and the trunk. These nodules are usually painful and are associated with fever, malaise, nausea, vomiting and some loss of weight. The reaction occurs at frequent intervals or, in the more chronic form, remains active for long periods. In untreated cases the temperature comes down by lysis. With repeated acute attacks or in the more chronic form, there is a tendency for the lesions to develop pustulation and for chronic induration of the skin to occur. This is particularly seen in lepromatous cases and in 93 per cent of them after the institution of sulfone therapy. The reaction may be so severe that sulfone therapy may have to be discontinued. In this process, if the nerves are involved, it can be very painful. We diagnose leprosy neuritis by its longer duration and it may cause loss of nerve function. Histological studies of erythema nodosum lesions show vascular changes in the small subcutaneous blood vessels and their branches in the corium. These vessels show endothelial proliferation and there is oedema and infiltration of cells and inflammation in the perivascular areas. The most characteristic change is the marked oedema in the corium.

The reaction may be an allergic response to sulfone or Herxheimer reaction. In the past this condition was treated with Fuadin (Stibophen) with dramatic relief. But Fuadin is ineffective in repeated acute episodes or in the chronic forms. In these cases either adrenal steroid hormones or adrenocortico steroid hormone had been used. It has been tried in 10 cases. The cases are reported in detail. It was noticed that no serious complications had occurred as a result of treatment in the usual doses. With higher doses and when used for longer periods, it is better to control electrolyte and water disturbances. Hormones are particularly useful in the early resistant cases. There is a possibility that some of them might have subsided spontaneously but the response was so quick and dramatic that such a possibility is not very likely. The hormones are particularly useful in the treatment of leprosy neuritis. They may fail where irreversible changes have taken place and are particularly useful in preventing drug addiction and in controlling the pain. The use of cortisone has resulted in converting the nerve to a normal appearance.

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### **CYSTINURIA AND CYSTINOSIS (LIGNAC-FANCONI SYNDROME)**

J. B. Mehta

Cystinuria has to be distinguished from cystinosis. In the former cystine along with other amino acids is excreted in the urine. Its importance lies only in the fact that cystine calculi are formed. The two diseases are probably separate entities, though cystinuria has been reported in relatives of patients suffering from cystinosis. In cystinosis the defect seems to be abnormal deposition of cystine crystals in the tissues of the body. In the cornea they are detected by slit lamp examination; marrow puncture smears may reveal the crystals or lymph node biopsy may reveal them<sup>3</sup>. Various other amino acids are excreted in the urine. Most probably the defect is

## Cytology, Exfoliative

of either amino acid metabolism or renal tubular dysfunction, but cystine is deposited in the tissues<sup>1,2,3,4</sup> because of its relative insolubility.

Clinically these cases present in infants who do not thrive, are stunted, rickety, hypotonic, have polyuria, osteoporosis and albuminuria, glycosuria, and photophobia. Mild urinary infection may be present. A low blood phosphorus and potassium level, but raised alkaline phosphatase and blood urea are found. Toni-Fanconi syndrome and cystinosis are related<sup>4</sup>. The rickets are very resistant to treatment. There is no effective treatment for the disease.

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## CYTOLOGY, EXFOLIATIVE

J. C. Anguli

The greatest field for usefulness of exfoliative cytology apparently lies in the field of cervical cytology. Vaginal smears may be used in which case the cells are exfoliated, or direct cervical smears may be used, in which the cells that are examined are living cells scraped from the cervix ; hence the term exfoliative is not strictly accurate in all instances. The cervical smear is at its best in the diagnosis of carcinomas *in situ* of the cervix. Fairly good evidence exists that at times certain instances of cervical carcinoma *in situ* have later become infiltrative. However, considerable disagreement is present among pathologists as to what constitutes carcinoma *in situ* of the cervix. Siegler sent 25 pathologists a group of 20 slides that represented difficult and borderline problems in the histologic diagnosis of carcinoma *in situ* of the cervix. Complete diagnostic agreement was not obtained on any of these slides. Every individual slide was believed to represent a malignant lesion by at least one observer. The definitive answer to this problem is not easy. Obviously, many years of research work will be necessary before there is complete understanding of these changes in cervical epithelium.

Less useful fields for exfoliative cytology include the lung and pleural and peritoneal fluids. However, carcinoma of the lung only, occasionally is diagnosed solely on the basis of cytologic examination. Evidence of a pulmonary lesion in the lung usually is present in thoracic roentgenograms, a fact that by itself, renders an operation imperative; also positive results of bronchoscopic biopsy are more accurate than are positive results of cytologic studies. However, the finding of cancer cells in sputum or bronchial secretions certainly lends weight to a clinical impression of pulmonary carcinoma. Positive results of the cytologic examination of ascitic fluid are falsely positive in at least 5 per cent of cases, so this technic is not completely reliable. It is highly questionable whether much value can be attached to routine cytologic examination of lesions of the skin, oral cavity, rectum, or breast. Examination of gastric material, regardless of whether or not a mechanical device is used for abrading the mucosa, is of questionable practical value.

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## DEAFNESS, END-ORGAN

J. V. DeSa

**Diagnosis and Significance :** The term end-organ deafness has been accepted in current literature to replace the terms "cochlear deafness", "inner ear deafness", and "inner ear conduction deafness". This took place after Mygind, in 1947, recognised two divisions of perceptive deafness : that of end-organ origin and that of nervous origin.

The characteristics of hearing associated with end-organ deafness are :

1. Variation in degree of hearing loss.
2. Deafness associated with elevated bone conduction threshold.
3. Loudness recruitment of high degree.
4. Adaptation.



5. Reduced discrimination for speech presented at high intensities.
6. Lowered threshold of pain.
7. Diplacusis binauralis dysharmonica.
8. Variations in the difference limen for intensity.

**Pathology :** Histological studies on experimentally induced end-organ deafness revealed that smallest damage detected was stripping of the mesothelial cells from the undersurface of the organ of Corti. The external hair cells were next involved. Progressively severer changes were separation of the organ of Corti from the basilar membrane, break in the continuity of organ of Corti, rupture of reticular membrane with oozing out of the external hair cells and finally complete disappearance of the organ of Corti. Degeneration of nerve cells and fibres in the spiral ganglion began later.

End-organ deafness is most commonly found in Mènière's disease but is found to be absent in 2 phases of the disease : in the period of remissions during which the hearing becomes normal and in late states when it is assumed that nerve cells in the spiral ganglion degenerate.

End-organ deafness is characteristically absent in cases of lesions involving the acoustic nerve, but may be present during early stages of the acoustic neurofibroma when pressure of the tumour causes more disturbances of the circulation than of nerve function.

End-organ deafness is also found in certain cases of deafness of sudden origin. Vascular dysfunction of the cochlea is assumed to be the cause of this hearing loss ; often it is the occlusion of the cochlear artery or one of its branches.

On reviewing the literature on sudden deafness, Hallberg noted several possible causative factors, such as :

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| 1. Thrombosis, spasm of vessels or haemorrhage ; | 4. Toxic labyrinthitis ;                |
| 2. Neuritis of the eighth cranial nerve ;        | 5. Emotional episodes ;                 |
| 3. Systemic disease ;                            | 6. Injection of " orthobiotic serum " ; |
|  | 7. Mènière's disease.                   |

In 89 out of 178 cases, the cause was vascular ; in 56 it was Mènière's disease ; in 17 undetermined, in 15 miscellaneous and in one functional.

In the light of this knowledge, it is advisable to treat the patients of sudden deafness of end-organ type vigorously for Mènière's disease in the hope that irreversible changes have not already taken place in the cochlea. Prognosis is poor in patients who have been deaf for two months or more as far as acoustic function is concerned. It is better comparatively for the vestibular component.

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#### DEATHS, SUDDEN AND UNEXPECTED

D. Bhaskara Reddy

Clinicians frequently encounter patients who die unexpectedly without premonitory symptoms. These patients may have been in excellent health until the very time of death. In many such cases there is no suspicion of poisoning or foul play. Because of unexpectedness of death and previous good health of the individual the case may be referred to the coroner. Abrupt death brought about by pathological changes which might have been severe but which did not reveal clinically recognisable symptoms is referred to as unexpected death from natural causes. Often insignificant factors may lead to untimely death. Fright, emotion, or exertion of slight degree, that is likely to raise the arterial pressure may precipitate the fatal end in patients with coronary lesions. Careful recording of case history, searching autopsy inclusive of histological examination of all organs and appropriate laboratory investigations of body fluids would not only disclose a clinically latent morbid lesion but also the immediate cause of death.

Reddy and Reddy<sup>2</sup> from Visakhapatnam, (1955), in a detailed study of 26 necropsy cases have indicated the various causes of unexpected death over a period of 10 years. They concluded that the incidence of unexpected deaths attributable to pathological lesions of cardiovascular system, respiratory system and miscellaneous group are nearly equal while the recorded percentage incidence for each is 42, 23, 13 respectively and are of the opinion that conditions like infective hepatitis, cerebral malaria and filariasis could also account for unexpected deaths in the tropics and should always be borne in mind. Reddy and Rao (1957)<sup>3</sup> have recorded two



## Diabetes Mellitus, Cardiovascular Complications in

cases of unexpected death, one due to a ruptured syphilitic aneurysm of the ascending portion of the aorta and another due to a perforated peptic ulcer.

Unexpected deaths in infants and young children are commonly met with and many of them are found dead in bed. The interpretation of necropsy findings in infants dying unexpectedly while in apparent good health has received considerable attention in recent years. Werne and Garrow (1953)<sup>4</sup> studied 31 cases and in 28 of these cases diminution of the alveolar space, congestion, oedema, haemorrhage, collapse of the lung tissue and cellular haemorrhages in the thymus and bronchopulmonary and cervical lymph nodes, congestion and petechiae of viscera were seen. These vascular and lymphatic reactions are regarded in a sense nonspecific as they also occur in anoxia, infective or allergic conditions. Microscopically some degree of bronchitis or bronchiolitis is present in every case. Adelson and Kinney (1956)<sup>1</sup> under the auspices of the U.S. Public Health Service, carried out an investigation at the Western Reserve University School of Medicine, Cleveland, Ohio, into the cases of sudden and unexpected death occurring in 126 infants and children between the ages of 10 days and 2 years. No less than 85 per cent of the children were under 7 months. Sexes were equally represented. In more than 83 per cent of the cases there was evidence of inflammation of varying degrees of severity in the respiratory tract and acute haemorrhagic pulmonary oedema was frequently present. There was also a total lack of anything suggestive of status lymphaticus or any other abnormalities of spleen, thymus gland or lymph nodes to which sudden death in infancy was often attributed to in the past. In none of the cases unsuspected congenital abnormalities were seen.

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**DENTAL CARIES, CALCIUM FLUORIDE AS PROPHYLACTIC IN—***See* RICKETS AND  
**DENTAL CARIES, CALCIUM FLUORIDE AS PROPHYLACTIC IN**

**DERMATOLOGY—***See* SKIN DISEASES

## DIABETES MELLITUS, CARDIOVASCULAR COMPLICATIONS IN L. K. Ganguli

There are many autopsy studies of arteriosclerosis and coronary artery disease in diabetics. Study of cardiac symptoms and the prevalence of the heart disease are few. Liebow et al<sup>1</sup> have studied the cardiac status of 383 diabetic patients, over 40 years old. They found 161 (42 per cent) patients suffering from arteriosclerotic heart disease of which 62 (16.2 per cent) had arteriosclerosis of the aorta in addition. Myocardial infarction occurred in 26 (6.8 per cent) and 10.2 per cent suffered from angina pectoris. In 4 patients (2 with a previously normal E.C.G.) suffering from myocardial infarction there was no history of any acute episode. These cases were detected on routine E. C. G. examination. There was positive relation between arteriosclerosis and hypertension in these diabetics. Premature degenerative vascular disease is now the most common hazard in diabetes. Proper control of diabetes is an important factor in the prevention of these degenerative changes and they are in direct proportion to uncontrolled or poorly controlled diabetes. The incidence of degenerative vascular disease in comparable groups of 121 known and 146 unknown diabetes as found by Parkhurst and Betsch<sup>2</sup> is shown in the table.

The main factors in the development of vascular complications are the age of the patient and the duration of the disease. In a review of 5,000 cases by Reinhardt et al<sup>3</sup> 213 patients had diabetes mellitus and only 57 had both diabetes and hypertension. Patients having both were somewhat older. Another interesting observation was that a high degree of obesity (86 per cent) was present in this group. Vascular complications were four times higher in the combined group. Commenting on the management of the cases the authors mention that it is essentially the management of each disease separately. NPH insulin and hypotensive drugs have been favoured by them along with reduction of obesity.

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The arteriosclerotic process is essentially the same regardless of the vessels involved. It commences earliest in the aorta. Cerebral arteries are more regularly involved in comparison to other vessels. Shuffstall<sup>4</sup> made 87 autopsy studies of arteriosclerotic diabetic patients. Marked changes were present in the heart in 29 patients, in the brain in 10 and in the kidneys in 3 patients. Arteriolar sclerosis of the peripheral vessels, particularly that of the retinal vessels was correlated to the duration of diabetes.

TABLE SHOWING INCIDENCE OF DEGENERATIVE VASCULAR DISEASE

Degenerative changes	Known diabetics (121 cases)		Previously unknown diabetics (146 cases)	
	No.	Per cent	No.	Per cent
Generalised arteriosclerosis .. .. .	13	10.7	13	8.9
Arteriosclerotic heart disease .. .. .	19	15.7	24	16.4
Coronary sclerosis .. .. .	8	6.6	12	8.2
Coronary thrombosis .. .. .	3	2.5	4	2.7
Cerebral arteriosclerosis .. .. .	4	3.3	6	4.1
Cerebral thrombosis .. .. .	1	0.8	5	3.4
Peripheral vascular disease .. .. .	10	8.3	6	4.1
Nephrosclerosis .. .. .	6	4.9	3	2.1
Hypertensive heart disease .. .. .	21	17.3	36	24.6
Hypertension only .. .. .	10	8.3	7	4.8
Patients manifesting degenerative vascular disease ..	67	55.4	85	58.2

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## DIABETES MELLITUS AND ITS COMPLICATIONS, MANAGEMENT OF

G. B. Mankad

The management of diabetes mellitus can be carried out by diet alone or by diet and administration of insulin or the oral antidiabetic drugs. Vitamins and lipotropic agents are used as adjuncts. In the pre-insulin days, before 1920, graduated diets with restricted carbohydrates and periodically even fasts were the only therapeutic measures that were employed. Even today diet remains an important basis of treatment. Based on her experience of the observation of 10,000 diabetics during the period of the last World War at the Diabetic Centre in Berlin, Hella Bernhard<sup>1</sup> begins treatment of the diabetics who have no acidosis by a schedule of three strict days. On the first day, the diet allowed consists of vegetables, lean meat, fish, eggs and cheese. On the second day, 250 g of oat-meal or rice, and 30 g of fat are added, distributed in 5 meals during the day, with 2 apples or oranges or bananas. The third day is like the first. Then carbohydrates are permitted in the light of the blood and urine findings. If the diabetes is not controlled within 2 or 3 weeks of such a regime, she introduces hypoglycaemic drugs supplemented by the special diet. She advocates sufficient carbohydrates, 1 g of protein per kg of body weight and very small quantities of fat, with total daily calories kept low. Within certain limits, the above proportion of fats, carbohydrates and proteins are not considered so important as the total caloric intake.

In uncomplicated diabetes the formula of Duncan<sup>2</sup> to estimate the basal caloric requirement seems very practical. It is as follows:

The ideal body weight in lb  $\times 10$  = Daily basal caloric requirement.

Add 100 to 200 calories if the patient is a young tall male,

Deduct 100 to 200 calories if the patient is an elderly short female.

Deduct 200 to 400 calories if the patient is obese.

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Then add 30 to 75 per cent of calories according to the nature of patient's activities, to finally arrive at the daily caloric requirement.

Then the proteins would be allowed 1 g per kg of body weight, or 1.5 g if the patient is young. The carbohydrate allowance has to be determined by trial in each case in consideration of the total calories permitted, and whether or not insulin is being used. The balance of the calories not provided by the proteins and carbohydrates is made up by fats, which have to remain restricted. Duncan also recommends the total intake to be distributed in 4 or 5 meals. If a long-acting insulin is being given the patient should take a small feed at bedtime to avoid hypoglycaemia during sleep or in early morning hours.

With the wide list of exchangeable foods at the disposal of the diabetic, the monotony is abolished. The diet prescriptions are made up in household measures so as to make the use of a weighing scale unnecessary. Low calorie diet is not recommended for juvenile diabetics and for diabetics with infections, e.g. tuberculosis.

The management of diabetes by insulin is the treatment of choice when the diabetic is a child, or an adolescent, or is suffering from an acute infection, or is in a seriously decompensated metabolic condition, or when an obese diabetic is not satisfactorily controlled by diet and oral hypoglycaemic drugs.

The problem whether or not the diet is to be restricted when insulin is given is discussed in a report by Kinnear and Dunlop<sup>3</sup> on the use of 'free diet' by 50 patients aged 9-71 years, studied for 5 years. Clinical control was achieved in 39, but the insulin requirement tended to rise. With the attendant dangers of the large doses of insulins the free diet regime is considered unwise.

Each of the different types of insulins has specific time and duration of action. The time of injection, the dose, the type of the insulin, and the diet—not only for proper effect, but for safety as well—should be tailored to fit each patient accurately. The smallest effective dose adjusted with the diet should maintain the weight 10 lb below the ideal weight for the patient's age and height. It should not give hypoglycaemic reactions. It should not allow the level of blood sugar to be more than 200 mg per cent and should keep the amount of sugar passed in urine in 24 hrs. under 10 g. A single injection of lente insulin daily, stabilizes over 85 per cent of diabetics, probably due to a well-hit proportion of 3:7 of the rapid and slow acting insulins<sup>4</sup>.

Mild diabetics may respond to one daily dose of ultralente or protamine zinc insulin. If the diabetic is not controlled with 20 units of slow-acting insulins, a combination of slow and rapid-acting insulins should be given. When the slow-acting insulin is given in a large dose singly or in combination, some bedtime nourishment must be given to guard against the early morning hypoglycaemia occurring during sleep which can go undetected, untreated and be even fatal.

Moderate diabetics can be controlled by one daily injection of N.P.H. or lente insulin. If the total units required in a case exceed 40, its mixture with ordinary or semilente is given. Once regulated by blood sugar tests, further adjustments in the dose and the type of insulins can be made in the light of glycosuria in the fasting and the post-prandial samples of urine.

The insulin therapy is adjusted to obtain a *clinical* and not a *chemical* control and therefore, with fasting blood sugar less than 120 and the post-prandial level of about 200 mg per cent no attempt need be made to render all the urine samples aglycosuric, lest hypoglycaemic conditions may develop which may lead to vascular degeneration similar to hyperglycaemia. If a diabetic under insulin treatment suffers from intercurrent infection, his insulin requirement increases, and to meet this, large doses, preferably of a rapid-acting insulin should be given.

Hypersensitivity to insulin has been known even with the lente varieties, but it is less pronounced than with P. Z. or N.P.H. insulins. Similarly, cases of insulin resistance have been recorded. The latter may develop in association with an acute infection. Presland and Todd<sup>5</sup> investigated a woman aged 57 who required 35 to 50 units of insulin. When she had a minor staphylococcal infection she needed as much as 5000 units of insulin daily.

**Management of Diabetes with Oral Antidiabetic Drugs:** The discovery of BZ 55 (carbutamide), and D 860 (tolbutamide) has brought oral antidiabetic therapy within the range of practical therapeutics. Further researches in this direction should help to simplify the long-term management of the diabetic state. In future all diabetics of recent development and aged 40 or over, are likely to be put on the oral treatment if diet alone fails to control the faulty metabolism.

The criteria for selection of the present diabetics for the treatment with the oral drugs are<sup>6</sup>: The age at the onset of diabetes should be over 45 years; the duration of the disease should not be longer than 5 years; the post-prandial blood sugar level does not exceed 250 mg per cent; the duration of insulin treatment, if being taken, is less than 2 years; the daily requirement of insulin does not exceed 40 units. With further experience the above criteria are relaxed.

As with insulin, the diet continues to be of primary importance in the management of diabetes with the oral antidiabetic drugs. Free unrestricted diet cannot be advised.

The Diabetic Centre in Germany<sup>7</sup> treats every case, provided he is not a juvenile diabetic or is not seriously decompensated, with diet alone and then if required adds the oral antidiabetic drug to the regime—insulin being brought in when the oral therapy fails. The Centre reports at present 40,000 diabetics under treatment with the oral antidiabetic drugs<sup>8</sup>.

The dosage of the oral antidiabetic drug has more or less a fixed range unlike the dose of insulin which varies from patient to patient and in the same patient from time to time.

The dose of carbutamide is 5 tablets daily for two days, then 3 tablets daily for next two days, then 2 tablets daily from the 5th to the 14th day. After two weeks the dose required may vary from  $\frac{1}{2}$  to 2 tablets a day. This maintenance dose is given as long as may be necessary.

The dose of tolbutamide is 2 tablets t.d.s. for 2 days, then 1 tablet twice daily on the third and the fourth days, then 2 tablets twice daily for 10 days. After two weeks of treatment, one tablet once to thrice may be given according to requirements. The entire daily dose of carbutamide can be given at one time, but tolbutamide should be administered in two or three divided doses.

The blood sugar curve behaves with both BZ 55 and D 860<sup>9</sup> nearly the same way<sup>10</sup>.

Carbutamide causes some euphoria which is not observed with tolbutamide<sup>11</sup>.

The blood sugar estimation and the urine tests should of course precede the institution of this treatment. They should be repeated on the fourth and again on the 15th day. In the light of the findings the regime may be modified and thereafter the urine examination daily or every few days should be a sufficient guide and the blood examination may be necessary every few weeks or even months.

Crowley et al<sup>12</sup> studied 42 diabetic patients treated with tolbutamide. Thirty patients who responded were maintained on this treatment for 6 weeks, and the drug was then discontinued. Only one of the 18 newly diagnosed diabetics of this group of 30 relapsed in 7 months of observation. If however, the remission in the newly diagnosed cases is so long, it is unjustifiable to continue the drug for an indefinite period and particularly when the drug remains equally effective during a relapse, should it take place.

If resumption of treatment even by insulin becomes necessary, Jacobi and Kammarath<sup>13</sup> have shown by trial in 97 cases that it can be done, since the course of antidiabetic drugs once given does not produce any adverse effects on the residual endogenous insulin production.

The untoward reactions of sulpha group of drugs, viz. leucopenia, skin rashes, hepatic or renal damage, have been recorded in as many as nine per cent of cases treated with these two drugs<sup>14</sup>. Allergic reactions are less common with tolbutamide as compared with carbutamide, but the gastro-intestinal tolerance of carbutamide is better<sup>15</sup>.

It seems that the Anglo-Saxon races are probably more susceptible to these reactions than the Germans<sup>16</sup>. The Aryans should resemble the Germans in this respect.

*Management with Oral Antidiabetics and Insulin Combined*: Some patients' response to diet with oral antidiabetic drugs is inadequate as shown by glycosuria persistent in the post-prandial sample which therefore necessitates at least two insulin injections a day. Such diabetics could be treated with one injection of insulin and one small dose of the oral hypoglycaemic drug to replace the second insulin injection. In this way the dose of each of the two agents is reduced and the untoward reactions are therefore lessened<sup>17</sup>.

Similarly, some diabetics whose occupation entails frequent travelling may be treated with insulin injections while they are at home but by oral drugs while away<sup>18</sup>.

*Non-specific Adjuncts used in the Management of Diabetes*: The diabetics in general need have a rather liberal supply of vitamins to maintain their proper metabolic balance. Vitamin B-complex, vitamin B<sub>12</sub>, vitamin C and vitamin E, deserve special mention. Prof. Wilhem Stepp<sup>22</sup> cites Svhröeder who demonstrates that glycosuria of depancreatized dogs could be checked only when vitamin B-complex was combined with insulin. For neurological

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disturbances of diabetes, Sancatta et al<sup>23</sup> consider 15 to 30  $\mu$ g of vitamin B<sub>12</sub> daily for a week or two followed by the same dose once or twice a week for maintenance as the most effective schedule. The anti-infective property of vitamin C makes it a valuable drug in diabetes which predisposes the sufferers to infection. Besides, Banerjee<sup>24</sup> at the Indian Science Congress (1952) confirmed the insulin-sparing action of this vitamin which he reported. This is further confirmed<sup>21</sup>. With 25 mg of vitamin C the insulin dose could be reduced to half but the carbohydrate in the diet could not be increased unless 100 mg of this vitamin was given. Marney and Rabii<sup>25</sup> are inclined to believe that 10 g of vitamin E given 4 hours before the usual dose of P. Z. insulin in two diabetics suppressed the blood sugar throughout the day, and remarked that this, if established, could modify the treatment of diabetes. The dose of 10 g of vitamin E is too large and will increase the cost of the regime but smaller doses may probably do as insulin-sparers.

The oral antidiabetic drugs are entirely useless as therapeutic agents in the management of the acute episodes of diabetes.

Gross and Greenberg<sup>19</sup> used sodium salicylate to prevent glycosuria. Joslin<sup>20</sup> commented on the rarity of diabetes coexisting with rheumatic fever. Reid James et al<sup>21</sup>, as a result of a study of 8 cases of diabetes, one of whom had coexisting rheumatism, report aspirin to have antidiabetic properties. He, on investigation of tolerance tests, found that all these 8 cases had their blood sugar curves lowered during administration of aspirin and fasting blood sugar well reduced. The aspirin would thus be a very useful oral antidiabetic, if the side effects like nausea, vomiting and ketosis could be prevented by some corrective agent, or by striking the dosage schedule which is effective to control the diabetes without producing these untoward effects of salicylism.

The necessity of using lipotropic drugs is felt from Goodman's<sup>23</sup> findings who says that 9 per cent of 459 cases of well-controlled diabetes, 60 per cent of uncontrolled diabetes, and 100 per cent of those with acidosis, showed an enlarged liver. The lipotropic drugs recommended are choline, methionine and betaine; the latter, with a low-fat diet, has an insulin-sparing action<sup>27</sup> and also hypotensive effect, making it a particularly useful agent in diabetes with hypertension.

Ajgaonkar<sup>28</sup> has worked at the J. J. Hospital Diabetic Clinic on the treatment of diabetes with Indian Ayurvedic drugs viz., a *bhasma* containing 22 mg of zinc, iron stannum with traces of cobalt and iron and 5 mg of mica. The zinc seems to be the principal element. Okamoto<sup>29</sup> has commented on the role of the presence and amount of zinc in the beta cells of the islands of Langerhan, in the genesis of diabetes.

Lakholia<sup>30</sup> tried on himself two drachms of *karela* juice twice a day, on empty stomach, increasing it to 1 oz twice a day for two months—insulin being discontinued, and made himself aglycosuric in 15 days.

**Management of Complications of Diabetes:** The frequency of complications and their severity are in inverse ratio to the efficiency of control of the diabetic state.

**Ketosis and Coma:** Severe ketosis without actual coma i.e. precoma<sup>31</sup> is treated as coma. The family doctor should render first aid only—then the patient should be transferred to a hospital for attention by a team of skilled specialists. If there be vomiting, abdominal pain or distension, gastric lavage with sodium bicarbonate solution should be done. If the patient be unconscious, this should be carried out with the patient placed in prone position with his head over the table so that the mouth is on a lower level than the larynx, to prevent the fluid running into the trachea and the bronchi. The insulin, soluble only, in the dose of 50 to 100 units according to the degree of ketosis, should be injected, part intravenously and the rest subcutaneously. Then in order to determine the subsequent treatment the following investigations should be carried out<sup>32</sup>.

1. Blood is taken every 4 hours for estimation of sugar, plasma acetone, CO<sub>2</sub> combining power, specific gravity and urea estimation during the time the patient is unconscious.

2. Urine for culture and routine examinations once on admission and then every 2 hours for rough estimation of sugar and acetone.

3. E. C. G. on admission and then every 4 hours for 24 hours as a guide to the recognition and treatment of hypopotassemia.

Insulin in doses from 50 to 100 units spaced from an hour to 4 hours as required should be given during the time the patient remains critical. When the consciousness has returned and

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the acetonuria has disappeared the nourishment by mouth can be resumed and the schedule of insulin should then be as under :

With 4 plus glycosuria 30 units every 2-4 hours.

With 3 plus glycosuria 20 units every 3-4 hours.

With 2 plus glycosuria 10 units every 4 hours.

With 1 plus glycosuria omit insulin.

During coma, to replace the fluids and salts lost give 2000 c.cm of normal saline in the first 2 hours, or more if the sp. gr. of whole blood is over 1055. Repeat this as required until the return of consciousness. Then broth, strained cereal, sweetened tea, and later on fruit juices could be given and the intravenous infusion reduced in proportion as indicated by the record of the intake and output.

After 4 hours of this therapy KCl g one every 4 hours, should be given so long as the E. C. G. shows hypopotassemia provided urine excretion is free. For children the dose is relatively smaller.

To avoid hypoglycaemia resulting from the large doses of insulin required during coma, 1000 c. cm of 5 per cent glucose in normal saline is given beginning 6 hours after the first dose of insulin and repeated every 6 hours until the nourishment is taken orally and retained. Investigations carried out at the University College and the Middlesex Hospital<sup>33</sup> in London, about the usefulness of fructose in diabetic ketosis have not revealed any advantage of fructose over glucose. Administration of alkalis is not always necessary, but to relieve the air hunger, molar sodium lactate infusion may be given to raise the CO<sub>2</sub>-combining power to 30 vol. per cent. However the whole blood transfusion is preferable to restore both the base and blood volume.

**Diet :** With the acute ketosis overcome, liquid diet for a day or two is yet necessary and then the usual home diet permissible to the patient in his diabetic state is given, spread in four or five meals.

If infection accompanies coma or is the cause of it the proper antibiotics should be given.

**Infections, Tuberculosis and Diabetic Carbuncle:** Diabetes and infection can each be the cause and result of the other, *vis-a-vis* the seed and the tree. Infection increases the insulin requirement of a diabetic and soluble insulin in repeated doses has to be given along with antibiotics. The latter sometimes control the infection rapidly and with each consequent fall in the insulin requirement, unexpected hypoglycaemia, resulting from the previous dose of insulin, may develop. This possibility should be kept in mind. With acute infection complicating diabetes, the patient should be given high caloric diet with adequate carbohydrates covered with sufficient insulin. This holds good in the case of tuberculosis with diabetes, where the patient's weight should be maintained at 5 or 10 per cent above the ideal weight for his age and height.

For carbuncle, besides the systemic antibiotics, topical applications of saturated magnesium sulphate compresses and of antibiotics are used. Mankad<sup>34</sup> is impressed with the early relief of pain and subsequent progress of healing following exposure of the carbuncle to superficial X-ray therapy once or twice a week.

**Pregnancy and Diabetes :** A diabetic woman when pregnant should be treated with diet and with or without hypoglycaemic agents. The oral antidiabetics have not yet been evaluated. Progesterone and diethylstilbestrol are recommended by Priscilla White et al<sup>35</sup> in a well-defined dosage schedule, and are believed by them to reduce the incidence of toxæmia, hydramnios and foetal mortality. A clinical trial carried out by the Medical Research Council of Great Britain on the use of these hormones does not confirm these results<sup>36</sup>. Termination of pregnancy at 38 weeks is advisable as the risk of foetal death increases after this time. Caesarean section is usually recommended<sup>37</sup>, unless the patient is a multipara with prospect of easy delivery, in which case induction of labour and vaginal delivery may be tried. Pedersen et al<sup>38</sup> concluded, on a study of 235 cases, that with proper control of diabetes and with conservative obstetric management and antenatal care of not less than 53 days before term, the foetal mortality was 10 per cent, against 33 per cent with the antenatal care given for less than 53 days—the overall mortality of foetus being 38 per cent. Therefore they think that it is unnecessary to give sex hormones or to do many caesarean sections. They stress the long term treatment and supervision by a physician during the last months of pregnancy.

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In later months of pregnancy some of the foetal insulin may be available to the mother and so the dose of insulin to the mother may be adjusted accordingly.

Treatment of ophthalmic complications includes control of the diabetic state by diet and by the hypoglycaemic drugs.

The neurological disturbances are best handled by the antidiabetic treatment supplemented by vitamins B<sub>12</sub> and B-complex factors.

That the duration of diabetes and the period of inadequate control are the aetiological factors of most of the complications, is the prevalent opinion.

So far we discussed the management of individual cases of diabetes. For the management of diabetic population there should be diabetic camps and diabetic centres for early diagnosis and treatment. These centres should be equipped with a laboratory and out-patient clinic for periodical check-up of the patients, the daily treatment being carried out by local practitioners under guidance of the centres. The centres should have a hospital to house decompensated diabetics or diabetics with acute complications, those needing initial regulation of diet or insulin, or for selection for the treatment with oral antidiabetic drugs available now.

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## DIABETES MELLITUS, TREATMENT OF, WITH INSULIN (ALSO SEE ANTIDIABETIC DRUGS, ORAL)

M. N. Guruswami

Diabetics are now divided into two groups—(1) The obese diabetic, usually middle-aged or elderly, showing little response to insulin and not liable to develop ketosis, called the stable, insulin-resistant type. (2) The thin, underweight, younger age group, much more sensitive to insulin, and unless properly controlled, quickly becoming ketotic, called the brittle or labile, insulin-deficient type.

Although plasma insulin is markedly reduced in the underweight, insulin-sensitive diabetic, the plasma of the obese diabetics contains about the same amount as that of normal subjects. (Bernstein and Lawrence, 1951)<sup>2</sup>.

The obese types usually do well with weight reduction by low calorie diet and exercise and as they do not suffer from insulin lack, it is not physiological to treat them with insulin. In the treatment of diabetics, due to primary insulin insufficiency replacement therapy is necessary (Nabarro and Stowers, 1955)<sup>15</sup>.

Alivisatos and McGullaugh (1955)<sup>1</sup> classified 172 diabetics into stable and brittle groups and showed that degenerative complications were commoner in the stable group, although with the stable group there were fewer complications when diabetes was well controlled.

In the therapy of diabetics in whom insulin is indicated, the problem has been to find an ideal insulin with flexible, prolonged action whereby it should be possible with single injection to regulate the blood sugar throughout the 24 hours.

From the time Hagedorn (1936)<sup>6</sup> made use of protamine insulin to 1950, when again he prepared his N.P.H. (Isophane) insulin, the method of prolonging the action of insulin had been to combine it with an additional protein, such as protamine, histone, or globin. The duration of action of these modified insulins varied considerably. Due to their inflexibility, one had to suitably combine them with regular crystalline insulin to meet the individual demands. They had in addition an allergenic propensity due to the added protein, even though in many instances people exhibited allergy to the insulin itself. This resulted in the preparation of a group of insulins called the lente insulins by Hallas Moller and his co-workers (1952)<sup>8</sup>.

Type	Appearance	Action	Duration (hrs.)	Zinc (mg/100 U.)	Buffer	pH	Protein Type	mg/100 U.
Regular	Clear	Rapid	5-7	0-0.04	None	2.5-3.5	None	..
Crystalline	Clear	Rapid	5-7	0.016-0.04	None	2.5-3.5	None	..
Protamine zinc	Turbid	Very slow	36+	0.2-0.25	Phosphate	7.1-7.4	Protamine	1.25
Globin	Clear	Slow	18-24	0.25-0.35	None	3.4-3.8	Globin	3.8
NPH	Turbid	Slow	24-28	0.016-0.04	Phosphate	7.1-7.4	Protamine	0.50
Lente	Turbid	Slow	24-28	0.2-0.25	Acetate	8.1-7.5	None	..

Characteristics of commercially available insulins

From A. Marble (1957)<sup>12</sup>

In 1934, Scott<sup>17</sup> found that various metals were important in the formation of insulin crystals. This led to the discovery that while small quantities of zinc (1-2 mg /1000 units) failed to retard the action of soluble insulin, large quantities increased its length of action.

Increasing the zinc content alone to prolong the insulin action was regarded as impracticable because of the local reaction which resulted. Hallas Moller found however, that insulin in the presence of a very small quantity of zinc (1 mg/1000 units) was less soluble at the pH of blood than protamine insulin, provided that anions such as phosphates and citrates were not present. With the use of acetate buffer, he was able to prepare a suspension of pure insulin in media at the pH of blood in the presence of very small quantities of zinc. The length of action of such preparations varied with the form of insulin, whether pure amorphous, amorphous or crystalline, varying from 12-30 hours. The action of amorphous insulin is shorter than that of crystalline, the larger the size of the crystal, the greater the duration of action.

Two basic suspensions have been prepared, viz., "semi-lente" (insulin zinc suspension—amorphous), containing amorphous particles, with action upto 16 hours, while a suspension



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containing crystals, called "ultra-lente" (insulin zinc suspension-crystalline), had action upto 30 hours. These insulins are stable at the body pH and the particles do not alter in size; the two insulins can be mixed in various proportions and the resultant action is the same as that following two separate injections. A mixture of 30 per cent of the quicker acting amorphous and 70 per cent of the longer acting crystalline insulin, most commonly useful, goes by the name "lente insulin" (insulin zinc suspension). If necessary, the early or late action of the mixture can be intensified by the addition of more of the amorphous or the crystalline variety.

However, insulin zinc suspensions cannot be mixed with soluble, ordinary (regular) insulin with its pH of 3-3.5, for some length of time, because at the resultant low pH, the amorphous zinc particles would gradually change into crystals tending to prolong the action of such a mixture, instead of increasing its immediate response. However, it is possible to have promptness and rapidity of action by adding in the syringe, just prior to injection, an appropriate amount of ordinary insulin, without making any attempt to mix the two types in the syringe (Slayton et al, 1955)<sup>18</sup>.

Newly formed endogenous insulin remains in the beta cells of the pancreatic islets as an undissolved zinc compound which however, according to its dissociation constant, can maintain certain basic concentration of insulin in the blood. If the blood sugar level rises, various intermediary metabolic products may bind the zinc and thus liberate insulin. It is possible that lente insulin takes the place of the granules of the beta cells (Hallas Moller, 1954)<sup>7</sup>.

Extensive clinical trials have been made since the introduction of these insulins. Early reports claimed several advantages over the preparations previously used. (1) They might be less likely than other long-acting insulins to cause allergy since there were no added proteins such as protamine and globin. (2) They might provide a homogenous uniform small series of preparations, carefully selected to span the spectrum of timing needs of the diabetic population when given in single daily injections. (3) The selection of either the standard insulin zinc suspension (lente) consisting of 3 parts of amorphous to 7 parts of crystalline or more appropriate mixtures of quick acting amorphous and slow acting crystalline suspensions, may give better control in diabetics imperfectly controlled on other insulin regimes (Editor, Lancet, 1956)<sup>4</sup>.

Lawrence and Oakley (1953)<sup>11</sup> confirmed the prolonged hypoglycaemic action lasting for 24 hours, enough to control blood sugar of moderately severe diabetics throughout the day and without causing hypoglycaemia during nights. There were no general or local reactions.

Nabarro and Stowers (1953)<sup>14</sup> treating 22 diabetics, reported lente insulin to be unsatisfactory in 10 out of 19 patients and recommended suitable mixtures and strength (2 to 8 mixture) for British diabetics and laid emphasis on late afternoon or early evening meals.

A new diabetic can well be started on his insulin therapy with insulin zinc suspension but diabetic control will be less rapid than it would be with soluble insulin (Oakley, 1953)<sup>16</sup>.

Venning (1954)<sup>20</sup> reported satisfactory control in 29 out of 42 diabetics, using single daily injections. The dose had to be often higher than that of the insulin previously used, even when the previous treatment had been vigorous and insulin dosage pushed to the limit of tolerance. The carbohydrate of diet spread evenly throughout the later part of the day and a mid-afternoon meal are considered essential. Local allergic reactions were noted in 2 patients.

Jersild (1956)<sup>10</sup> reported satisfactory control in 96 per cent of his 1000 unselected diabetics on single daily dose of insulin zinc suspension, while Spencer and Morgans (1956)<sup>19</sup> reported success in 83 per cent of 200 cases, most of whom had found some disadvantage with their previous insulin treatment.

Slayton et al (1955)<sup>18</sup> treated successfully 100 patients. There were few reactions, e.g. discomfort at the site of injection, especially in children, probably due to the preservative, tricresol, which has now been substituted by methyl paraben (Marble, 1957)<sup>12</sup>.

A theoretical advantage claimed is that lente insulins not containing protamine, on prolonged administration, cannot have any deleterious effect on blood lipoids arising from protamine which is a heparin antagonist.

Lente insulins cannot be used for emergencies, for which soluble insulin is the only drug of choice. If the patient is found severely ill with ketosis, when first seen, it is advisable to start the treatment with repeated injections of soluble insulin. After a few days when the acute phase has been overcome, one may safely and with advantage switch over to lente insulins (Murray, 1955)<sup>13</sup>.

In changing the types of insulin in patients already regulated on NPH insulin, given either alone or with crystalline insulin, lente may usually be substituted dose for dose. A lower initial dose of lente insulin is suggested because of better diabetic control with less lente than NPH. Diabetic control is said to be smoother and insulin reactions fewer and milder in stable diabetic patients treated (Haunz, 1955)<sup>9</sup>.

In patients treated with protamine zinc insulin, allowance must be made for the prompt action and shorter duration of effect of the lente insulin. On the other hand, in patients who have been on globin insulin, the longer duration of action of lente must be kept in mind (Marble, 1957)<sup>12</sup>.

Fitzgerald et al (1954)<sup>5</sup> studying the effect on 30 patients of transferring to IZS, found that an increase in the total dose of insulin was required at the time of transfer.

The diabetic controlled with lente insulin is upset more easily by intercurrent infections and this requires a bold increase of insulin dosage by 20 per cent or more (Murray, 1955).<sup>13</sup>

The earlier claims of absence of reaction to lente insulins have been contradicted by several reports of toxic reactions. Haunz (1955)<sup>9</sup> reported localised allergic phenomena in a significant percentage of cases although less common than with other modified insulins. Hypoglycaemic reactions as severe as with other modified insulins were recorded in 9 out of 66 mild stable diabetics. He recommends in such cases the use of non-reactive special beef lente insulins.

Davidson (1956)<sup>3</sup> reported severe skin reactions with IZS. Multiple crystallisation of insulin has reduced considerably its ability to induce reactions, but the dermal factor, probably has not been removed in this case.

However, all are agreed that the incidence of these reactions is smaller compared to other unmodified insulins.

Marble (1957)<sup>12</sup> states that the use of lente insulin should be considered in patients beginning insulin treatment, in those in whom other types of insulin have not satisfactorily controlled and in those exhibiting allergy to other varieties of insulin.

The Editor, *Lancet* (1956)<sup>4</sup>, remarks that one complaint about the introduction of IZS has been that there are so many alternative insulins that life is very complicated for both the diabetic and the doctor. It is possible that if the IZS were discovered 20 years ago when Scott and Fisher described their work on the effects of adding zinc to insulin, there would have been no incentive to develop protein depot insulins.

Nabarro and Stowers (1955)<sup>15</sup> concluded regretting that the diabetic patients' dream might be of an insulin preparation that could be taken by mouth but that at that time there was no prospect of such a dream coming true. However, they were unaware of the progress to be made by the end of the year (1955), when the epoch-making discovery of the oral diabetic drug, BZ 55—a sulphonylurea derivative, was in the making.

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## Diaphragmatic Hernia

### DIAPHRAGMATIC HERNIA

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**Oesophageal Hiatus Hernia.**—Cooley, Grindlay and Clagett<sup>1</sup> describe three salient anatomic structures that must be dealt with in the repair of oesophageal hiatal hernia: muscular oesophageal hiatus in the diaphragm, fibrous phreno-oesophageal ligament, and serous peritoneal sac.

(1) The oesophageal hiatus is composed of two muscular crura which surround the lower part of the oesophagus and has the shape of a tear-drop, with the point of the drop posteriorly. This muscular collar is almost always derived in its entirety from a splitting of the right crus of diaphragm. The hiatus is strongest anteriorly because of decussation of muscular fibres from both crura to form a muscular sling or raphé that is almost unyielding. The central tendon of the diaphragm in close proximity further prevents enlargement of the hiatus in this direction. At the sides, muscular fibres of the hiatus are directed perpendicularly, thus strengthening it against gross lateral expansion. Posteriorly, the hiatus is virtually unprotected.

(2) The phreno-oesophageal ligament or membrane is a continuation of the fascia lining the inferior diaphragmatic surface as it passes through the oesophageal hiatus, to become attached to the fascia propria of the oesophagus. It supports the oesophagus and helps to prevent displacement of the oesophago-gastric junction above the level of the diaphragm. Actually the 'ligament' is a continuation of the same transversalis fascia which is so important in the pathogenesis of direct inguinal hernia.

(3) The peritoneal sac is almost always located on the anterolateral aspect of the upper portion of the stomach and lower part of the oesophagus. It never completely surrounds the hernial contents. The wall of the stomach usually forms a part of the hernial sac and hence the derivation of the anatomically correct term "sliding" hiatal hernia.

Madden<sup>2</sup> describes the anatomy of the oesophageal hiatal ring based on observations made in a dissection study of 15 fresh cadaver specimens. The right crus is longer, thicker and more tendinous than the left. As it ascends, it separates into superficial and deep muscle layers to form completely the oesophageal hiatus. The thin superficial layer forms the right margin of the hiatal ring and the thick deep muscle layer the left. Anteriorly, the margin of the ring is in close proximity to both the tendinous portion of the diaphragm and the inferior phrenic vein. Posteriorly, the hiatus is partially occluded by a thin veil of decussating muscle fibres and fibro-areolar tissue. The left crus of the diaphragm does not participate in the formation of the oesophageal hiatal ring.

Sprafka, Azad and Baronofsky<sup>3</sup> undertook a study to determine the fate of small oesophageal hiatus hernias discovered on Roentgenologic gastro-intestinal examination.

One hundred and forty-nine patients with small oesophageal hiatus hernias were followed for periods of time upto 18 years. Of 130 patients followed from one to five years, 17 (13 per cent) showed progression from small to large hernias. Of 19 patients followed for six or more years, 11 (58 per cent) showed similar progression.

Of 61 patients with large oesophageal hiatus hernia, 17 (28 per cent) showed evidence of serious complications such as ulcer in the herniated portion of the stomach, oesophagitis or oesophageal stricture either singly or in combination.

Berry, Holbrook, Langdon and Mathewson<sup>4</sup> studied 15 patients suffering from hiatal hernia. Pneumo-peritoneum was induced in three sittings at intervals of 48 hours and an average pressure in the abdomen of approximately 10 cm of water was maintained. At the end of this study, the patients were presented to the surgical service for repair of the hiatus hernia. The degree of improvement following surgery closely correlated with that gained by pneumo-peritoneum except in the instance of one female patient who had recurrence of her previous symptoms two months after surgery. The mechanism by which relief is obtained is not entirely clear. This method might well be a valuable technique for selecting patients who will benefit from surgery.

Maisel, Cooper and Glenn<sup>5</sup> have described pneumo-peritoneum in the management of oesophageal hiatus hernia as a diagnostic and therapeutic procedure, the latter specially in poor risk patients refractory to usual conservative measures. Five patients with intractable symptoms from hiatal hernia were thus treated with gratifying results.

Mixson and Woloshin<sup>6</sup> analysed 31 cases of oesophageal hiatus hernia found by Roentgenographic studies of 360 pregnant women. This type of hernia tends to occur in the multipara more often than in primigravida, in older than in younger patients, and to disappear postpartum.

Symptoms consist of heartburn, nausea and vomiting beyond mid-pregnancy, and belching or vomiting during late pregnancy.

Jaffe and Szabo<sup>7</sup> describe two cases of Saint's Triad (i.e., hiatus hernia, gallstones and diverticulosis) out of 25 patients with hiatus hernia admitted to hospital over a period of three years. Of the remaining 23 patients, 6 had diverticulosis as well. They collected reports of 48 cases of Saint's triad recorded in the literature.

Mobley and Christensen<sup>8</sup> describe 153 cases of oesophageal hiatus hernia detected in a population of 30,000 people, over a period of 13 years. Minimum prevalence rate was 5 per 1000, sex incidence, three females to two males, and mean age 57.7 years. Twenty-one per cent of the patients (32) were asymptomatic, and 79 per cent had symptoms related to hiatal hernia. Low substernal or high epigastric pain or distress was the most frequent symptom. Next was dysphagia, usually in the low substernal region.

Twenty-five per cent of this group of 153 patients, had chronic cholecystitis, 24 per cent peptic ulcer, 2.6 per cent carcinoma of the gastro-intestinal tract and 2.6 per cent associated coronary heart disease. Diagnosis was established by Roentgenologic methods in 6 per cent and incidentally during unrelated operation in 13 per cent.

*Technique of Operation:* Madden<sup>2</sup> prefers transthoracic route through the left eighth interspace. Phrenic nerve is temporarily paralysed and oesophageal triangle, the site of hernial protrusion, is exposed.

An inverted T-shaped incision is made in the posterior mediastinal and diaphragmatic pleura, flaps are retracted and oesophagus is mobilised by blunt digital dissection. The hernia is mobilised by scissor dissection, and the hiatal muscular ring clearly defined. A segment of the diaphragm in juxtaposition to the hiatal ring is tented by Babcock clamps and incised. The left index finger is inserted through this incision into the peritoneal cavity and through the oesophageal hiatus, into the hernial sac and overlying phreno-oesophageal ligament and peritoneum separately incised. The hernia is reduced, the oesophagus is displaced posteriorly and a 'crown' suture (No. D silk) is inserted anteriorly to approximate the muscle fibres of the right crus. The oesophagus is then displaced anteriorly and the posterior sutures are inserted to approximate the superficial and deep muscle fibres of the right crus.

The incision in the diaphragm is closed and the flaps of diaphragmatic pleura approximated by sutures of fine silk. Posterior mediastinal pleura is not sutured. A layer-closure of the chest wall with water seal drainage of the pleural cavity completes the operation.

The technique was used in a consecutive series of 8 patients. In a follow-up period extending from 4 to 18 months, the results obtained were completely satisfactory.

Woodruff and James<sup>9</sup> have presented transabdominal technique of repair of sliding oesophageal hiatal hernia and reported 11 cases treated by this technique. The principles of their repair confirm closely those of Allison. The peritoneum and the underlying phreno-oesophageal ligament are divided along the lateral and anterior borders of the hiatal ring, the excess sac excised and a cuff of ligament and peritoneum about one in. in width is left attached to the oesophagus. The muscular borders of the ring behind the oesophagus are approximated with interrupted silk stitches until the hiatus is reduced to a size that just admits the oesophagus without constricting it. The repair is completed by fixing the attached cuff of phreno-oesophageal ligament to the diaphragm around the lateral and anterior edges of repaired hiatus.

Niesche<sup>10</sup> presents his experience of transthoracic repair of 61 cases of hiatus hernia. Two cardinal features must be observed, namely, the gap between the two portions of the right crus of the diaphragm must be closed to prevent recurrence of the hernia, and the acute angle between the terminal oesophagus and fundus of the stomach which is normally present, must be re-created to prevent reflux of gastric juice, by fixing the fundus of the stomach to the dome of the diaphragm.

Cooley, Grindlay and Clagett<sup>1</sup> devised a technique for the incorporation of a prosthesis in the repair of hiatal hernia, experimentally created in dogs by dividing the phreno-oesophageal ligament and dilatation of the muscular hiatus. In the process of repair, a C-shaped piece of Ivalon (polyvinyl formol) was used as the prosthesis to enclose the terminal part of the oesophagus in its centre. An inner row of fine silk interrupted sutures attached the prosthesis to the fascia propria of the oesophagus, and an outer row to the muscular diaphragm. One of the

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dogs died in the early post-operative period (20 days) of the oesophageal obstruction. The remaining nine survived the operation uneventfully. These dogs were killed at intervals varying from six weeks to nine months from the time of surgery. On post-mortem examination, the repaired hiatus and Ivalon prosthesis exhibited almost unyielding strength.

Pai<sup>11</sup> describes a case of an oesophageal hiatus hernia with organo-axial volvulus of the stomach and strangulation, who was admitted in a moribund state and died within an hour. At autopsy, whole of the stomach was found in the left chest. Hernia had occurred through the oesophageal hiatus, abdominal part of the oesophagus was acutely kinked and doubled upon itself, greater curvature of the stomach was pointing upwards and the lesser curvature downwards. The stomach was grossly distended, congested and full of fluid and gas.

**Diaphragmatic Hernia Through the Foramen of Morgagni.**—Boyd and Wooldrige<sup>12</sup> refer to a monograph written in the eighteenth century, wherein Morgagni first described herniation through the retrosternal aspect of the diaphragm. In his cases, hernia protruded through the anterior part of the diaphragm behind the xiphoid cartilage. This aperture has since become known as the foramen of Morgagni.

The hernia is of acquired type and possesses a sac. It is rare in infants because of the relatively large size of the liver in early life, and short transverse mesocolon. Predominant occurrence on the right side may be due to larger attachment of the pericardium to the left side of the diaphragm. Occasionally the sternal attachment of the diaphragm is entirely absent and there is one large defect behind the sternum and adjacent costochondral junctions.

Nine cases of hernia through the foramen of Morgagni treated surgically at the Lahey Clinic have been reviewed. Out of eight patients operated upon, six were women and two men. One patient (female) had two operations for the hernia. In eight cases, the hernia presented on the right side and in one on the left. In the latter case, herniation on the left side developed within two years after a transthoracic repair of a rightsided Morgagni hernia.

Brigand and Merlier<sup>13</sup> describe three cases in which lipomatous masses were encountered in the region usually associated with hernias of the foramen of Morgagni. Pneumoperitoneum excluded diaphragmatic hernia. The mass was associated with an oval foramen of Morgagni communicating with the pro-peritoneal fat. The mass was easily removed.

Obersteg<sup>14</sup> describes a case of subcostal diaphragmatic hernia in a 48 year old woman who had abdominal complaints, dyspnoea and asthma. Diagnosis was established only at autopsy when a hernial sac, the size of a child's head and containing the greater omentum, was found passing through the right foramen of Morgagni.

Dor and Eymery<sup>15</sup> prefer to include all defects in the anterior attachment of the diaphragm to the chest under the term 'anterior diaphragmatic hernia'. They collected 189 such cases from the literature including 12 of their own. The peritoneal sac was always present. Incarceration or strangulation of the stomach, colon, or omentum occurred in five per cent of their cases.

Kuntzen<sup>16</sup> describes the technique of the closure of congenital anterior diaphragmatic hernia through a transthoracic route. The posterior margin of the hernial opening is identified and approximated to costal cartilages through mattress sutures. This technique has been followed in four cases with perfect satisfaction.

**Strangulated Diaphragmatic Hernia.**—Vira Reddy<sup>17</sup> has reported a case of strangulated diaphragmatic hernia through the foramen of Morgagni. The patient aged 56 years, was admitted to the hospital 30 hours after she suddenly developed severe pain in the epigastrium while taking her meal in a squatting posture, followed by vomiting. At operation, a loop of middle of the transverse colon was found to have gone through the foramen of Morgagni.

Joynt<sup>18</sup> describes a case of a 41 year old man with a history of sudden, severe, crampy abdominal pain for about 30 minutes, followed by dull, persistent, non-radiating pain in the epigastrium, nausea and vomiting. On thoracotomy a gangrenous necrotic mass consisting of stomach, was freed by blunt dissection and margins of constricting ring of the diaphragmatic hernia 4 cm in diameter, were freed alround. The hernia was of traumatic type with no definite sac. Resection of the extensive gangrenous portion of the fundus and body of the stomach was carried out and the defect in the diaphragm was repaired. Closed drainage of pleural cavity was provided.

Carter and Guiseffi reviewed 43 cases of strangulated diaphragmatic hernia in 1948 and noted that 85 per cent were of traumatic origin. An acute attack was precipitated by relatively sudden

increase in intra-abdominal pressure which usually occurred within three years of the injury. Pearson reviewed 31 cases in 1953 and reported 60 per cent to be traumatic in origin.

Gangrene of the stomach associated with diaphragmatic hernia is rarely encountered in literature. Hughes and associates in 1955, collected nine cases and reported one of their own. In this group of ten cases, two survived gastric resection.

Markle IV<sup>19</sup> has reported a case of strangulated right-sided diaphragmatic hernia in a 74 year old man admitted with severe generalised abdominal colic. Twentyfive years before, he had an automobile accident in which the left side of his chest was injured.

On laparotomy, a strangulated hernia in the posterior portion of the right diaphragm was detected. Most of the right colon was in the chest as were a few feet of distended ileum with a large Meckel's diverticulum. The right lobe of the liver which was atrophic, protruded through the diaphragm to the extent that the gall bladder, shrunken and full of stones, was just within the chest. The liver was apparently fixed in the chest forming medial and posterior walls of the hernia opening.

**Pleuroperitoneal Sinus Hernia.**—Thompson Wells<sup>20</sup> describes a case of a 28 year old male whose main complaint was that from childhood, he had always had vague abdominal pains especially marked in the left hypochondrium, with occasional attacks of diarrhoea. He had some difficulty in passing flatus and became dyspnoeic if he did not pass it for some time. He often heard a gurgling noise in the left side of the chest.

On left thoracotomy through the seventh intercostal space, the left side of the chest was found to be filled with the bowel. There was no hernial sac. The hernia had occurred through a patent pleuro-peritoneal sinus about 3 in. in diameter and consisted of spleen, almost all of the small bowel, ileo-caecal junction, the appendix and half of the large gut.

**Short Oesophageal Hernia.**—Burford and Lischer<sup>21</sup> chose Finney pyloroplasty as the procedure to ensure prompt and continuous gastric emptying for the treatment of short oesophageal hernia with oesophagitis. Sixteen patients were thus treated. Their ages varied from 46 years to 65. Nine were female and seven male. Symptoms of gastric reflux had been present for two to five years. Nine patients had one year follow-up. Fifteen cases had improvement and ten out of these experienced virtually complete relief from symptoms.

**Hernia of the Liver.**—Mario Borri<sup>22</sup> describes a case of his own of hernia of the liver through the diaphragm and reviews 34 published cases. Herniation may occur with or without partial eventration of the right dome of the diaphragm. Distinction between the two types may be very difficult but presence of an anomalous lobe of the liver may be a differentiating point.

**Compound Diaphragmatic Hernia.**—Brown, Moberg and Esser<sup>23</sup> present five cases of 'compound' diaphragmatic hernia (non-traumatic diaphragmatic hernia in which more than one organ have herniated through the involved foramen). Out of the five cases presented, hernia occurred through the hiatus in three cases, through the foramen of Morgagni in one and through the foramen of Bochdalek in one. Cardiorespiratory symptoms were severe in all the cases. Four of the five cases were operated upon with one fatality because of the need for massive resection of the entire small intestine and the right colon.

**Eventration of Diaphragm.**—Arnheim<sup>24</sup> described a case of eventration of the diaphragm, in a female infant aged eight days, who developed dyspnoea and cyanosis on the fifth day of extra-uterine life.

On laparotomy through a left oblique subcostal incision, the left leaf of the diaphragm was found to be high in the chest and represented by a thin translucent membrane except the anterior edge which showed a thin cuff of muscle.

Arnheim further reviewed eight cases of congenital eventration of the diaphragm reported in the literature. Six were boys and two girls. Their ages varied from 8 days to 13 months. Five were on the left side and three on the right. Symptoms in infancy were mainly respiratory, with varying degrees of dyspnoea and cyanosis, either constantly present or appeared only when respiratory reserves were needed.

The signs and symptoms of congenital eventration and hernia of the diaphragm may be exactly alike. The Roentgenologic and fluoroscopic examinations furnished the only means of differentiation.

Prompt surgical treatment should be carried out if dyspnoea and cyanosis are severe. In the eight infants treated surgically, the operative technique consisted essentially in pulling the

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diaphragm down to the level of the margin of diaphragmatic attachments and plication of the diaphragm with superimposed rows of interrupted mattress sutures of silk. The newly constructed diaphragm was fixed to the thoracic wall, crus of the diaphragm and renal fascia. The operative approach was thoracic in four infants, abdominal in three and thoraco-abdominal in one.

Fojanini and Monti<sup>25</sup> report 13 cases of right diaphragmatic eventration, which have been classified in three groups :

1. Total eventration which may be congenital or acquired.
2. Eventration located to anterior and medial portion of the right hemidiaphragm. This also may be congenital or acquired.
3. Partial eventration accompanied by morphological alteration of the liver.

Diagnosis is radiological with previous pneumoperitoneum. Plastic and prosthetic surgical methods have been successfully used.

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## DIET, LOW SODIUM

J. B. Mehta

Low sodium diet is advocated as a part of treatment in congestive heart failure, hypertension, renal diseases, cirrhosis of the liver, toxæmias of pregnancy, Ménière's syndrome and many other states. Prolonged use of such diets may lead to a deficiency of sodium in the body. In the U. S. A., there is a particularly close co-operation between the Council of Foods and Nutrition and the manufacturers of processed and canned foods. Nutritional values, including that



of minerals, are given on the labels. Thus it becomes easy for the attending physician to advise on the quantity of such foods to be taken<sup>1</sup>. Yet the hazard of sodium depletion in low-sodium diets is real and one must be on guard for its appearance. The sodium depletion syndrome is characterised by lethargy, dry inelastic skin, dry tongue, persisting or increasing oedema, with a low specific gravity of urine and low salt content, a fall in plasma volume and ultimately circulatory collapse<sup>4</sup>. The other dangers are deficiency syndromes of vitamins and proteins, as the diets are deficient in these elements. Yet the number of reports on sodium depletion as complication are meagre.

This led Hulet to investigate low sodium diets<sup>2</sup>. He analysed 13 different, so called "200 mg sodium diets." These diets were calculated from tables commonly in use in the U.S.A. Analysing them for sodium content by the filtrate method, he found all of them to be faulty, the sodium content ranging from 304-812 mg. Only the Kempner rice-fruit diet was below 200 mg. This shows the fallacy of relying exclusively on accepted tables of composition. Much of the discrepancy may come from the variation in salt content of tap water used, from place to place.

Lal and Chowdhary<sup>3</sup> estimating iron contents of foods in Bihar found different figures from those of the Indian Health Bulletin, 1951. They stress that various kinds of foods vary in their mineral content, according to local soil conditions, salt content of water in that part, etc.

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## DYSENTERY, AMOEBIC

N. S. Variava

The term "amoebiasis" means infection with *Entamoeba histolytica*. It is not synonymous with "amoebic dysentery". Amoebiasis is a systemic disease and diarrhoea is not necessarily one of its manifestations. It covers all lesions caused by this organism.

Amoebiasis is very common in the tropical countries. In India it is so common that hardly a person has escaped the infection in his life time. Fortunately many get over the infection. In some it persists and causes a great amount of suffering and invalidity.

**Incidence:** No reliable statistics are available of the incidence of infection in India. In America where sanitary measures are strictly enforced, the rate of infection has been stated as 20 per cent<sup>1</sup>. Lamb<sup>2</sup>, Conybeare and Mann<sup>3</sup> report that in England the incidence is very high. But they give no figures. The high incidence is due to a large number of symptomless "cyst-passers." Variava<sup>4</sup> quoting hospital figures puts down the incidence at 1.4 per cent. But these figures are about patients who came to hospital with symptoms suggestive of amoebiasis, and who on further investigation had positive stool findings. The figures for asymptomatic carriers are not available.

It is not the desire of the reviewer to discuss in detail the various aspects of amoebiasis, but it is essential to have a clear idea of its pathology, symptoms and signs and the modern trends in treatment. Variava<sup>5</sup> has summarised these trends and salient features.

**Some facts about Pathogenesis:** (1) Spread of the infection is from "hand to mouth". Flies play a role in the spread of the infection.

(2) Vegetative forms live in the walls of the ulcers. Once passed out they soon die. Cysts on the other hand are resistant. When ingested the cyst wall is dissolved by the intestinal juices and the vegetative organism reaches the colon.

(3) Intestinal bacterial flora plays a very important role in establishing the organisms in the colon. In their absence, the amoeba cannot get a foothold in the colon. Phillips, Wolfe, Rees, Gordon, Wright and Reymers<sup>6</sup> confirm this role of intestinal flora in the pathogenesis of amoebiasis.

(4) In the intestine, the lesions are almost completely localised to the colon, mostly in the caecum, ascending colon, hepatic and splenic flexures. Ulcers are also found in the sigmoid



## Dysentery, Amoebic

colon, rectum, and anal canal. The ulcer openings on the mucous membrane is small, but there is extensive undermining in the deeper submucosal and muscular tissues.

(5) Systemic infection, i.e. infection of liver, lungs, etc. usually follow intestinal lesions. The vegetative organisms in the submucous layer, which is very vascular and from where the radicles of the portal vein arise, are carried by the portal blood vessels to the liver. In the liver they produce hepatitis and even hepatic abscess. Freedman and Cleve<sup>1</sup> put down the incidence of liver involvement upto 56 per cent of clinical cases of amoebic dysentery. Hepatitis may be present in the acute, subacute and chronic forms. Variava<sup>4</sup> quotes the incidence of liver involvement of cases of amoebic dysentery for the years 1951 to 1954, 1951—15 per cent, 1952—18 per cent, 1953—20 per cent and 1954—35 per cent. And he comments on the alarming increase in the incidence of amoebic dysentery and of hepatitis and hepatic abscess.

(6) Systemic infection, e.g. of liver, lung, brain, skin, etc., can also occur without involving the intestine at all. Freedman and Cleve<sup>1</sup> put down direct extra-intestinal spread at nearly 20 per cent.

(7) The catalytic toxins of *Entamoeba histolytica* produce necrosis in the tissues, and this necrosis is responsible for formation of ulcers and granulomatous masses in intestine (amoeboma—Radke<sup>7</sup>). Such masses are most common in the rectum and anal canal<sup>6</sup> and invade the skin. Skin lesions can also occur after drainage of an abscess, or secondary to a colostomy.

Abscesses also form in the liver, lungs and brain. Amoebic abscesses of the brain though rare are reported. Upto now 88 such cases are recorded<sup>6</sup>.

(8) Newcomers to the tropics are more liable to infection and in them the infection is more severe. The local residents have some amount of immunity to infection, though no immune bodies have been isolated.

**Symptoms :** A few simple facts about symptoms are worthy of note<sup>5</sup>. (1) During the acute attack the diagnosis is easy. Insist on seeing the stool. They have a peculiar foul odour, which is characteristic. Stools contain blood and mucus.

(2) Subacute cases cause difficulty in diagnosis. History is often suggestive. Attacks of diarrhoea containing a little mucus in the stools, follow meals or dietary indiscretion. This is followed by long periods of intermissions.

(3) Chronic cases are most difficult to diagnose. They can be divided into three or four sub-groups, as far as the clinical symptoms are concerned.

(a) Asymptomatic cases—they form the largest group. Most of the patients are silent carriers, who unconsciously spread the infection.

(b) Patients getting very vague abdominal symptoms, e.g. a little abdominal gripe, followed by a sensation of stool, and relief after evacuation. This occurs off and on. The stool usually does not contain blood or mucus. Often it is well formed, or at the most soft.

(c) Patients presenting symptoms suggestive of chronic appendicitis. Many of these patients have been operated without showing any improvement.

(d) Patients in whom the presenting symptoms are gastric, mostly of a dyspeptic type. Many of these patients are for years treated as dyspeptics.

(e) Cases in whom the presenting features are marked wasting. The patients are markedly emaciated and many such patients are suspected to be suffering from cancer or tuberculosis. Time and again the author<sup>5</sup> has stressed that such patients show marked improvement after a course of emetine and other drugs.

(4) Radke<sup>7</sup> describes the symptoms of amoeboma of the intestine. There is intermittent diarrhoea containing bloody stools. This comes with cramp like lower abdominal pain. There is low grade fever, malaise, and loss of weight. A tumour mass may be felt in the intestine, and such amoebomas may be present in any part of the colon, from caecum to anal canal. Most commonly they are found in the rectum and anal canal, where a mass may be palpated on rectal examination. When the skin is involved, there is severe pain and tenderness in lower region.

(5) Hepatic amoebiasis occurs in two forms—plain hepatitis and hepatic abscess. Plain hepatitis may occur without any dysentery. When it follows dysentery, the dysenteric symptoms disappear. In many cases there is mild jaundice.

Hepatic abscess is easy to diagnose. Large amoebic abscesses of the liver often produce palpable masses in the epigastrium. They may grow as large as to be visible on gross inspection.

Abscess of liver may burst externally, or into the surrounding tissues, e.g. pleural cavity, lung, mediastinum, pericardium, or in peritoneum, stomach, colon, or other neighbouring structures. About 13 per cent rupture into the peritoneum<sup>1</sup>.

(6) Pneumonic amoebiasis may be a direct systemic extension to lung, or may result from liver abscess bursting into the lung. These cases can be mistaken for dry pleurisy, pleural effusion, empyema, or pneumonitis.

(7) In chronic exacerbating amoebiasis, excessive fibrosis may cause cicatricial stenosis of the bowel. This may simulate cancer clinically. It may occur as a localised narrowing, or involvement of great length of intestine, and give rise to symptoms of partial or complete obstruction.

(8) Amoebic abscess of the brain is often associated with liver or lung abscess or metastasis in the brain may occur after surgery on liver abscess.

*Diagnosis* : Diagnosis may often be very difficult. In doubtful cases resort to—

(1) History—past history of diarrhoea or dysentery is important, particularly in the tropics.

(2) Stool examination—should always be done. In chronic cases, the author<sup>4,5</sup> recommends the following method. Give emetine gr 1 in the morning and a saline purgative the same evening. Examine all the stools. *E. histolytica* are more likely to be present in later stools. Stool examination should be done within half an hour after passing.

Recently a new species of amoeba which is non-pathogenic to man but which closely resembles *E. histolytica* in its general morphology and also in producing quadri-nucleated cysts has been reported. It was first discovered in Russia in 1943 and is named *E. moskkovskii*<sup>6</sup>. This organism has created new problems in diagnosis. It has long been recognised that in England a large number of people are carriers of amoeba, but have never suffered from dysentery. Is it possible that in view of this finding, the organism in question is *E. moskkovskii*, and not *E. histolytica*?

(3) Sigmoidoscopy should be done. Undermined ulcers with normal intervening mucous membrane is suggestive. A scraping taken from the ulcer may show the vegetative amoeba.

(4) Screening of the chest will show diminished movement of diaphragm in hepatitis. A high and immobile diaphragm is suggestive of a liver abscess. A distinct bulging of the diaphragm, merging into the shadow of the lower lobe of the lung is definitely diagnostic.

(5) MacLean and Drew<sup>9</sup> suggest blood sedimentation rate. Raised E. S. R. is suggestive of hepatic involvement.

*Treatment* : Treatment should aim at complete destruction of *E. histolytica*. It should constantly be remembered that both the cystic and vegetative organisms co-exist in the same individual. Hence the drugs must destroy both these forms of the organism. Unfortunately no single known amoebicidal drug can give complete cure. Various drugs have got to be combined to produce the maximum cure rate. This is reviewed in detail by the author<sup>4,5</sup>. Amoebicidal drugs can be divided into three groups:

(1) Those having specific action against the organisms lying in the intestine, e.g. emetine hydrochloride, iodo-hydroxy quinoline products, and arsenical preparations.

(2) Drugs having specific action against the organism in systemic infections of liver, lungs, etc. These drugs have no action against intestinal forms. To this group belongs antimalarial drugs, e.g. chloroquine. Emetine hydrochloride is also useful in this group.

(3) Drugs having no direct amoebicidal action, but which act by inhibiting the intestinal flora which help *E. histolytica* to flourish. They have no action against systemic infection. To this group belong the broad-spectrum antibiotics.

**Emetine hydrochloride** : It is still the most potent drug for treatment of amoebiasis. It acts on vegetative organisms, both in the intestinal wall and in systemic infections. It has no action on cysts. Deep intramuscular injections of gr 1 should be given for six days. In some patients it produces marked weakness. It even affects the heart and causes myocarditis. To prevent side effects combine it with vitamin B<sub>1</sub> 100 mg or strychnine. Emetine should be given in the evening only and the patient should rest after the injection. Cure rate is about 70 per cent.

**Emetine bismuth iodide** : is not much used these days. As it causes gastric irritation it is given in gelatine capsules. The dose is gr 1 on the first day, gr 2 on the second day and then gr 3 daily for 10 days. It is not recommended for routine use.

## Dysentery, Amoebic

**Iodo-hydroxyquinoline products :** The common products employed are diodoquin, entero-vioform and chiniofon (Yatren). These iodine containing drugs are effective against intestinal organisms only—both cystic and vegetative forms lying free in the lumen of the bowel. Cure rate is about 60 per cent. Combined with emetine it gives the cure rate of 80 to 85 per cent.

**Arsenical preparations :** Arsenical preparations, e.g. carbarsone, and milibis, by themselves have limited value, cure rate not being more than 30 per cent. Besides, these are toxic drugs and are contra-indicated in renal disease.

**Antimalarial drugs :** To this group belong chloroquine, its diphosphate (Aralen), and its sulphate (Nivaquine). Even Atebrin is recommended. They have effective range of action against both intestinal as well as systemic infections. As chloroquine is concentrated to a marked extent in the liver, it is strongly recommended for hepatic amoebiasis. It has no contra-indications and practically no toxic effects if used in proper dosage. Used alone, it is effective in 80 to 90 per cent cases. One tablet three times a day for two weeks, and then once a day for further one or two weeks is recommended. Chloroquine has little action in amoebic dysentery, as it is rapidly absorbed from the intestinal tract.

Abdel Gheffar and Abdel Gheffar<sup>10</sup> recommend mepacrine (Atebrin) for amoebic hepatitis and hepatic abscess. From 0.3 to 0.9 gram should be given daily for 10 days. They consider this drug superior to chloroquine.

**Antibiotics :** Antibiotics commonly used are: (1) tetracycline (Achromycin), (2) chlortetracycline (Aureomycin), (3) oxytetracycline (Terramycin), (4) erythromycin (Ilotycin), (5) chloramphenicol, and (6) fumagillin. With the possible exception of the last, they have no direct action on *Entamoeba histolytica*, but attack the intestinal flora. In the absence of the intestinal flora, the amoeba cannot gain a foothold in the colon. They have no action in systemic infections.

Woodruff<sup>11</sup> has compared the anti-amoebic effect of the antibiotics with emetine bismuth iodide oral therapy. He feels that the antibiotics by themselves have not much to recommend.

Fry, Brock and Weinstein<sup>12</sup> conclude that of all the tetracycline preparations, Terramycin is the best. Dose recommended is two capsules of 250 mg each, every 6 hours for 10 days. Woodruff<sup>11</sup> recommends tetracycline for resistant cases.

Elsdon Dew, Wilmot and Armstrong<sup>13</sup> after extensive trials of fumagillin conclude, that to be successful, 200 mg of fumagillin should be given daily for 10 days. 62.5 per cent successes are reported.

On the whole fumagillin and even Bacitracin are not prescribed alone.

**Other Drugs:** Glaucarubin (Merck, Sharp and Dohme) is a new amoebicidal drug, which is promising in its results<sup>9, 11</sup>. It is given in daily dose of 0.2 to 0.6 grams for 10 days. Out of 25 cases treated with this drug, only three relapsed.

It will be seen from the large number of amoebicidal drugs, that no single drug is effective against all types of infection. It is now universally accepted that combination of various drugs should be done. Variava<sup>5</sup> recommends emetine, iodo-hydroxyquinoline and chloroquine. In severe cases antibiotics may also be combined. By this combination he claims 90 per cent cure rate. Fry and his associates<sup>12</sup> recommend Terramycin, or chloromycetin, with iodo-hydroxy quinoline and chloroquine.

Whatever combinations are tried, repeat the treatment once or twice at intervals of two to three months.

**Post-dysenteric Syndrome :** Fierst and Werner<sup>14</sup> studied the post-dysenteric syndrome in 150 unselected cases of both amoebic and bacillary dysentery. Majority of cases were of amoebiasis. The patients complained of abdominal pains, varying from mild to severe gripe. Such pains remained for days to weeks and then disappeared. In a year there may be three to four such attacks. Chronic diarrhoea is also common. An important feature of the post-dysenteric syndrome is the increased bowel response to various nervous and psychic stimuli. There is even increased gastro-colic reflex. Such patients become neurotic and sensitive to certain types of food. But this is mainly a psychological effect.

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## DYSENTERY, BACILLARY

N. S. Variava

The term "dysentery" is commonly used to indicate an abdominal condition associated with loose motions, containing blood and mucus. Such loose motions may be due to many causes. Thus several varieties of flagellates give rise to dysentery. In the Tropics, *Giardia lamblia*,—a common parasite of the small intestine can cause dysenteric symptoms. *Balantidium coli* also causes dysentery. But the term is reserved for two intestinal infections : (1) Bacillary dysentery—due to various types of dysentery bacilli of the genus *Shigella*, and (2) Amoebic dysentery—due to *Entamoeba histolytica*.

Bacillary dysentery, like typhoid fever is a good index of the sanitation of a place, and of the sanitary habits of its people. It occurs where people conglomerate, and as a result there is lowering of the sanitary habits, e.g., places of pilgrimage, occasions of festivals, in institutions, etc. Throughout history, outbreaks of dysentery have been common in armies in the field.

Bacillary dysentery is spread by water, milk, and food contaminated by an infected person, or by flies. Thus "finger, food and flies" are chief aetiological factors. The germs are transmitted through mouth to the intestine. In the large intestine they cause marked hyperaemia of the mucous membrane. Later on there is formation of ulcers on the mucous membrane, due to necrosis of the lymphoid follicles of the large intestine. The ulcers, pin point in size at first may expand and form large ulcers. The mucous membrane becomes very congested and friable.

*Incidence* : Variava<sup>1</sup> quoting hospital figures from 1950 to 1954, puts down the incidence as follows : 1950—0.9 per cent, 1951—0.6 per cent, 1952—0.3 per cent, 1953—0.7 per cent, 1954—1 per cent. Owing to improved sanitation, epidemics of bacillary dysentery have become less frequent. But sporadic cases occur from time to time, and at intervals mild epidemics still occur, specially at places where many people collect together, and thus lower the sanitation. Bacillary dysentery is not a disease of the tropics. It is common in temperate zones also. No country is exempt. All ages and both sexes are susceptible.

Fairley<sup>2</sup> suggests that more than half of the dysentery of the warm climates is caused by organisms of the Flexner-Boyd group.

*Clinical Types* : Clinically, the disease manifests itself into five types—(1) Acute fulminating dysentery. There is severe diarrhoea—stools varying from 20 to 50 per day. Stools contain blood and mucus. There is severe cramp like pain all over the abdomen. Temperature shoots up to 104°F to 105°F. Patient is markedly toxic. As a result of frequent large watery stools, he becomes dehydrated. There is often oliguria and strangury. Vomiting may follow and the case may resemble food poisoning. Delirium, coma and collapse may set in and the patient may die. Hiccough is always a bad sign.

(2) Moderately severe type : There is diarrhoea—10 to 20 stools per day. Fever ranges from 101°F to 102°F. Abdominal pain of griping type is followed by stools containing blood and mucus. Anus becomes excoriated and painful. But the patient does not look ill. There is no prostration or weakness.

(3) Mild or asymptomatic dysentery : There is mild colic and a few stools. There is usually no fever and no blood and mucus in the stools. In some patients such mild attacks of diarrhoea may occur after some indiscretion in diet. Attacks of diarrhoea which occur among visitors to tropical countries, and which are regarded by the sufferers as a matter of course, are in reality mild bacillary dysentery.

## Dysentery, Bacillary

(4) Chronic dysentery : There are bouts of colicky abdominal pain with diarrhoea. The patient becomes emaciated and pale, with hollow cheeks. The abdomen is scaphoid and tender on palpations. The colon is spastic and thickened. This type of attacks lasts for a day or two, and then disappears. After some weeks there will be another attack.

(5) Atypical forms : This is the most important group, as the original disease may be completely missed. Appendicular, meningeal and pneumonic types are described. Here the predominating symptoms resemble those of appendicitis, meningitis or of pneumonia. But together with these, the patient gets mild diarrhoea—only two to three stools per day, and stools contain blood and mucus.

*Diagnosis* : Variava<sup>1</sup> lays great stress on naked eye examination of the stool. The appearance of the stool is characteristic. There is usually no faecal matter. The stool has a peculiar mucoid smell, not necessarily offensive. There is a lot of mucus, mixed with blood, giving the appearance of red currant jelly.

Stool examination and sigmoidoscopy help to settle the diagnosis. A slide made from the mucus shows R. B. C.'s, few pus cells, and occasionally macrophages.

*Treatment* : Bacillary dysentery like typhoid fever is an infectious disease. Complete rest in bed must be enforced till the patient becomes free of all symptoms, e.g., fever, diarrhoea, abdominal pains, etc.

*Diet* : Must be liquid. Give fluids generously. In severe cases give intravenously, by drip method, 3 to 4 pints of 5 per cent glucose, or give it subcutaneously. Give it by mouth if the patient can retain it. Milk is usually not well tolerated, and is best avoided. Half normal saline, fruit juices, whey, buttermilk, or glucose drinks should be given by mouth. Give feeds more frequently where fluids are tolerated by mouth. Encourage the patient to take sufficient quantities of fluids orally. As the patient improves, prescribe a well balanced, low residue diet containing high protein and vitamin content. Jellies and strained soups, eggs, fish, meat and vegetables can be safely given.

If there is severe loss of blood, give 300 to 350 c.cm of blood transfusion. Blood transfusion is also required if the patient is collapsed.

*Drugs* : Chemotherapy must be begun immediately, preferably with a little absorbed sulphonamide, e.g., Formo-cibazole—2 tablets 4 hourly or phthalyl sulphathiazole—2 tablets every four hourly. Continue until the diarrhoea completely stops.

So far as the bacteriostatic effect on the dysentery organisms is concerned, there is little to choose between absorbable and the poorly absorbed sulphonamide preparations. American practice favours sulphadiazine—two tablets four hourly. British practice, and most of the Indian practice favours sulphaguanidine—four tablets four hourly, or other little-absorbed sulphonamide preparations. There is danger of anuria with sulphadiazine. So a high fluid intake of about five pints in every twenty-four hours is essential. With poorly absorbed sulphonamide preparations we need not fear this complication.

In severe cases associated with dehydration, a broad-spectrum antibiotic should be used in preference to a sulphonamide preparation, e.g., chloramphenicol, or one of the tetracycline derivatives. Some strains of dysentery bacilli are resistant to sulphonamides, and if a case treated by one of the sulphonamide preparations fails to respond in two or three days, switch over to broad-spectrum antibiotic treatment. In a severe case give one capsule of 250 mg by mouth every four hourly. Keep this dosage for two or three days. A cure will follow in practically every case. After that continue one capsule every eight hourly for another two or three days. Broad-spectrum antibiotics are especially useful in children. But these drugs are not without danger. Staphylococcal and fungal enteritis may ensue. In such cases there should be immediate cessation of the antibiotic treatment, and an alternative preferably a sulphonamide should be substituted. When patients are to be treated with a broad-spectrum antibiotic, especially when such treatment is intensive or protracted, combine the antibiotic with Mycostatin (Squibb), one tablet of 500,000 units t. d. s. Continue it as long as the antibacterial agent is given. It is preferable to continue it for three or four days after the antibiotic is stopped.

Bismuth preparations, or kaolin are not used nowadays. Similarly opiates are not very much used. We still make use of the opiates in cases where the patient complains of severe abdominal pain, or as tincture opi enemata to check excessive diarrhoea. Before trying opiates for severe griping abdominal pain, try application of warmth to the abdomen.

Serum is also not used nowadays. Its only indication is acute fulminating dysentery due to Shiga infection. For an adult, give in first twenty-four hours 50,000 to 100,000 units intravenously. Add the polyvalent serum (50 to 100 c.cm) to an intravenous drip and give it slowly at 30 to 40 drops per minute. Before giving the serum intravenously, the sensitivity of the patient to serum must always be tested. Intravenous administration is liable to cause severe reactions. Hence 40 to 80 c.cm should be injected subcutaneously into the abdominal wall. It can be repeated after twenty-four to thirty-six hours.

With modern treatment chronic cases are rare. In all chronic dysentery cases, suspect amoebic infection. Appropriate treatment for amoebiasis should be given. Many chronic cases present symptoms of ulcerative colitis, and they should be treated on the same lines.

Variava<sup>1</sup> recommends the following treatment in chronic cases. After a bowel wash, a retention enema of sulphaguanidine 8 tablets well crushed, and suspended in 4 oz. of water is given per rectum through a catheter by the drip method. It must take 15 to 20 minutes to finish 4 oz. of the enema, and it must be retained for half to one hour. Give it morning and evening for 8 to 10 days.

If the patient continues to pass mucus in stools, give tannic acid (65 grains in a pint of water) enema for rectal irrigation.

**Prophylaxis :** MacLean and Drew<sup>3</sup> lay great stress on control measures for bacillary dysentery. The stool being a potent source of infection should be disinfected prior to disposal. Repeated macroscopic and microscopic examination of the stool should be done throughout the disease. Patients should not be discharged until three stool cultures are negative.

Fletcher<sup>4</sup> recommends the following control measures : (1) Sufferers from the disease must be isolated and steps taken for disinfection of excreta. (2) Anti-fly measures must be instituted. Food is covered, and all garbage is disposed of regularly. Latrines must be made fly proof. Spraying the walls with 5 per cent D. D. T. in kerosene is effective in reducing the fly population. (3) Personal precautions include cleanliness of the hands, avoidance of raw foods and vegetables. (4) During an epidemic or when an outbreak occurs in an institution, pay particular attention to food handlers. Any person with intestinal upset should be withdrawn until bacteriologically proved safe. Phthalyl sulphathiazole may have prophylactic value.

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## DYSPHAGIA

S. Sachdev

**Congenital Dysphagia:** Persistent dysphagia in an adult with no gross anatomic abnormality should suggest a search for a serious cause. Intracranial haemorrhage, oedema, hypoxia, anoxia, or developmental disorders of the nervous system may be the cause. Seymour R. Cohen<sup>1</sup> has reported 13 cases of congenital dysphagia, where the defect was of neurogenic origin. He emphasizes the diagnostic value of X-ray examination and fluoroscopy in defects of neuromuscular function. Management of such cases has been described.

**Dysphagia Lusoria:** Eleven cases of this malady have been described<sup>2</sup> and dysphagia lusoria was the only congenital abnormality in these. Dysphagia lusoria is the name given to the condition arising from oesophageal compression by an anomalous right subclavian artery. The formation of this anomaly has been described and its incidence estimated to be from 0.6 to 1.8 per cent. It rarely causes symptoms and is often associated with other congenital defects. The significant data about these cases has been given. Radiological diagnosis is recommended and the treatment recommended is surgical but is rarely necessary. Importance of reassurance and explanation has been stressed.

A recent report<sup>3</sup> about this condition is from Calcutta. The author has described compression of the oesophagus in a male aged 60 by double aortic arch. Diagnosis was established by X-ray examination after barium swallow, in both the postero-anterior and lateral views. Angiocardiography was done to confirm the diagnosis.

**Roentgen Studies:** An evaluation of the effect of a parasympatheticomimetic drug, Urecho-line, and of an anti-spasmodic, Dibuline on oesophageal function in normal subjects and in

## Eale's Disease

patients complaining of dysphagia, was undertaken at the Temple University School of Medicine, Philadelphia. The subjects were studied in three groups :

- (i) Ten healthy subjects ;
- (ii) Ten patients with cardiospasm ;
- (iii) Twenty-three patients with other diseases of the oesophagus (oesophagitis, hiatus hernia with inefficient peristalsis).

Each subject was given 15 ml of a barium suspension to swallow and the time taken for transport through the oesophagus observed fluoroscopically was measured on 3 occasions. Five mg of Urecholine was then given subcutaneously and the process repeated 15 to 20 minutes later. Dibuline 30 mg was given subcutaneously finally and timings noted as soon as xerostomia was noticed and gastric peristalsis abolished. The results in this series indicate that Urecholine caused delayed emptying of the oesophagus while giving Dibuline resulted in slightly better oesophageal emptying. The effects of these drugs in the various groups have been discussed and compared with those already reported. They support the theory that in cardiospasm the lower third of the oesophagus is denervated and distinguish it from dysrhythmia of the oesophagus for which they recommend Urecholine 5 to 10 mg in water before meals or at bed time.

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## FALE'S DISEASE

S. P. Gupta

Eale's disease is much more common in India than in the West probably due to the high incidence of tuberculosis. It accounts for one third of all non-traumatic cases.

Mostly the patients belong to middle or poor class. In my review the ratio of male to female was 30 to 1, family history was negative in all the cases, the average age was 23.9 years, the youngest case recorded was that of a child of 13 years and the oldest was a man of 38 years. Some of these cases had healed tubercular glands in the neck or mediastinum. The condition to begin with occurred in one eye and in later stages the other eye was also involved in 75 per cent of the cases, the interval being six months to a year.

The typical features of Eale's disease are :

- (a) Changes in blood vessels—vasculitis and more precisely periphlebitis.
- (b) Haemorrhage—mainly pre-retinal which later bursts into the vitreous.
- (c) Proliferative bands appear in the later stages during absorption of vitreous haemorrhages, although the first or second haemorrhage usually being absorbed without any proliferative bands.

**Aetiology:** The main factor is supposed to be tuberculous periphlebitis though various other causes like septic foci, vitamin C deficiency and endocrinal disturbance have been mentioned. The disproportionate male involvement suggests endocrinal disturbance as an associated factor, with tuberculous periphlebitis causing at the periphery a neovascularization which may be intra-retinal, vitreal or rarely uveal ; the new vessels rupturing and causing the haemorrhage. Due to sudden loss of vision the patient usually consults the doctor immediately.

As regards the mode of infection there are two schools of thought :

One is that infection travels through the blood vessels and the organisms penetrate through small arterioles to perivascular tissues of small veins to cause periphlebitis. The other school maintains that infection gets lodged in the ciliary body reaching there via the blood stream, and then either the bacteria themselves or the toxins produced by them pass via the vitreous to act upon the blood vessels and cause periphlebitis.

Experimental work done by me, which is being still continued on rats, leads me to believe that histamine or an allied substance in the blood may affect the vessels and produce vasodilatation and haemorrhage inside the eye.

**Complications:** Retinitis proliferans is the end result sometimes causing retinal detachment. Rarely haemorrhagic glaucoma may occur after six to eight weeks.

**Treatment:** Considering the aetiology of Eale's disease it is advisable that apart from complete rest and nourishing diet and atropine drops one per cent b. d. to the affected eye, the patient should be given an extensive course or anti-tuberculous treatment with subconjunctival streptomycin one per cent, to be repeated on every 3rd day. Streptobion b. d. by mouth also helps in the absorption of haemorrhage. This treatment should be repeated again every fourth month for one to two years. The patient should also be advised to take light work and avoid constipation and trauma. Endocrine and X-ray therapy is not of much value.

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### EAR, CONGENITAL ATRESIA OF

J. V. DeSa

Formerly neglected, this condition has been tackled successfully in recent years after the works of Altman, Woodman, Omberdenne, Shambhaugh and others.

The usual finding in congenital atresia is complete bony closure of the ear with a bony ear drum and a deformed malleus and incus. The auricle is often deformed. Meurman classifies these combined lesions into 3 grades :

**Grade I :** Malformed auricles, smaller in size than a normal ear, with characteristic features of the auricle.

**Grade II :** Complete atresia of the canal with a rudimentary auricle, consisting of a low, oblong hook formed at the cranial end corresponding to the helix.

**Grade III :** Complete atresia with just a lobule to represent pinna.

Most cases belonged to Grade II in Meurman's series of 74 cases.

The extent of pneumatization of the mastoid bears some relationship to the grade of malformation ; the third grade microtia cases show a distinctly poor air cell system.

The incus and malleus are fused and clumpy in most cases, and the stapes is generally fixed.

The cases require elaborate investigations before embarking upon treatment. These investigations include radiological examination with Mayer's, Schuller's and Stenver's positions. Nasopharyngoscopy and Eustachian catheterization and an X-ray with the catheter in the tube also furnish important information. They not only enlighten one on the pathogenesis, but also orient the surgeon.

If the condition is bilateral, surgical intervention must be done to prevent intellectual backwardness from co-existent speech defect. An air and bone conduction audiogram is necessary before operative treatment. Surgery is primarily directed to improve conductive hearing loss after being certain of normal cochlear function and pneumatization of mastoid process. The best age for correction of congenital atresia is between 2-4 years.

Endaural surgery of the involved ear is preferred. Entering the antrum the deformed ossicles and the bony drum are removed. Mobility of the stapes must be determined. A split thickness graft is allowed to lie against the stapes. If the stapes is fixed fenestration has to be considered.

Facial nerve generally adopts an abnormal course in such cases and palsy is likely to complicate the good result if scrupulous care is not exercised to protect it.

Elaborate operative procedures have been described and the technique has to be modified in every case to meet the individual demands.

Reconstruction of the pinna by various stages is described but the final results have been so unsatisfactory that the use of prosthesis is now preferred.

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**EAR DISEASE, FACIAL NERVE IN—See FACIAL NERVE IN EAR DISEASE**

**EAR DISEASE, INTRACRANIAL COMPLICATIONS OF—See INTRACRANIAL COMPLICATIONS OF EAR DISEASE**



## EAR, NOSE AND THROAT DISEASES, TREATMENT OF

C. A. Amesur

Modern therapy has been considerably influenced by our better appreciation of the physiology and immunology of the upper respiratory tract and the part played by allergy in many of them. The introduction of several potent remedies during the last 20 years have also been factors of importance.

Sulphonamide drugs are substitute derivatives of suphanilamide. New drugs are put on the market and some of them have shown remarkable therapeutic properties. Among the new sulphonamides, antibacterial action has been most approximated by sulphadiazine, sulphamerazine, sulphadimetine (Elkosin) sulfisoxazole (Gantrisin) or by a combination of them. Their degree of absorption, diffusion, excretion together with their solubility in urine differ widely. Henry S. Williams has summarised their use as under:

- (a) In presence of Gram-positive cocci and bacilli;
- (b) Adequate dose in susceptible cases is one grain for each pound of body weight in 24 hours.
- (c) Should not be used for mild infection or given for common cold.

Penicillin is the safest and cheapest of antibiotics. Its main disadvantage is its rather limited spectrum and the fact that the most effective way of its administration has been by injection. Parenterally it can be given in crystal form two to four times per day, as depot procaine penicillin, when its action lasts for 24 hours. Diamine with its action for 48 hours (6 lacs), diamine fortified 12 lacs for six days. Then there are oral forms. Phenoxymethyl penicillin (penicillin V) has recently been put on the market and has given satisfactory blood levels. It is prescribed by weight and the dose is 120 to 240 mg (equivalent to 200,000 to 400,000 units of soluble penicillin). There are topical forms for intrathecal, intrapleural and aerosol use. For local use powders and creams are available.

Amesur<sup>1</sup> at the 3rd Annual Conference of the E.N.T. Surgeons of India held at Calcutta emphasised that sulphonamides were bound to blood plasma but antibiotics were not. On the other hand antibiotics were able to penetrate blood coagulum—but sulphonamides were not. Nasal discharge is tested against the sensitivity to both penicillin and streptomycin and the required antibiotic is used locally as well.

**Tetracycline:** There are three members of this series. Tetracycline (Achromycin) and two derivatives, chlortetracycline (Aureomycin) and oxytetracycline (Terramycin). The average dose is 1 to 2 g in 24 hours in divided doses. The introduction of an antifungal agent Nystatin (Mycostatin) may prove of value in reducing the incidence of moniliasis following broad spectrum therapy. Moniliasis of mouth, anus and vagina are real dangers. A particularly dangerous complication is 'super-infection'. The bowel is invaded by staphylococci that are resistant to all chemotherapeutic agents.

Acute tonsillitis is best treated by penicillin; phenoxymethyl penicillin (penicillin V) 120 mg four hourly. More certain results are obtained by procaine penicillin, usually for 4 to 5 days. A recent well-controlled trial has shown that both in streptococcal and in non-streptococcal sore throats improvement sets in more rapidly when oral penicillin is prescribed than when no antibiotic is used. (Chapple A. P. L.). Acute sinusitis and acute otitis media are treated in the same way as acute tonsillitis. Tetracyclines are used in otolaryngeal practice when penicillin has failed.

Erythromycin is useful for Gram-positive organisms, specially for staphylococci that have been found on sensitivity tests to be resistant to other antibiotics. It is also used for the treatment of 'diphtheria carriers'. Dose is upto 2 g per day for adults. Polymyxin B used as a topical agent in Gram-negative organisms in otitis externa and in otitis media, specially by *B. pyocyaneus*. The suitable dose parenterally is 200,000 units 6 hourly. Streptomycin and dihydrostreptomycin are used in the treatment of tuberculous infection. The daily dose is 1 to 2 g. Neomycin is ototoxic and is not used.

Bacitracin is used where penicillin fails. Tyrothricin which contains gramicidin and tyrocidine is active against Gram-positive organisms. If brought in contact with sub-arachnoid tissues it can bring about chemical meningitis. Spiramycin and novobiocin are some of the recently introduced antibiotics awaiting full clinical evaluation.

Toxic reactions to antibiotics are rare. They may broadly be divided into : (a) Allergic and anaphylactic, from mild to severe.

(b) Gastro-intestinal : Pruritus, proctocolitis, superinfection in the small intestine with resistant staphylococci.

(c) Blood dyscrasias, Of which agranulocytosis is the most serious.

(d) Neurotoxic : Streptomycin on the vestibular apparatus and dihydrostreptomycin on the auditory nerve ; severe permanent damage can result.

(e) Renal hazards : Crystalluria, anuria and calculi formation ; most with sulphonamides.

ACTH and cortisone. Cortisone is used in preference to ACTH, as it can be orally administered. Dosage is 200 to 300 mg daily for adults in divided doses at intervals of not less than six hours. Prednisone and prednisolone are synthetic analogues and would appear to be equally efficacious. They are five times as strong and doses are proportionately less. Corticotrophin is used as a temporary substitute for those receiving cortisone for prolonged periods to obviate risks of adrenal atrophy. A dosage of 80 to 200 mg in divided doses six hourly, i. m. is adequate. A long-acting preparation in gel-form is available and is given only once in 24 hours.

These corticosteroids have been shown to have profound influence in many diseased processes affecting connective tissues. Effects are dramatic except in advanced renal disease. The disease may appear to be suppressed but the pathological process goes on. In E. N. T. practice these hormones have been used in the following pathological processes.

(a) Submucous fibrosis. Rao<sup>8</sup> as well as DeSa<sup>1</sup> have claimed beneficial results with the use of these hormones.

(b) In allergic reactions, angioneurotic oedema, severe forms of urticaria, bronchial asthma, and status asthmaticus. In laryngeal oedema, tracheotomy has been obviated by its use.

(c) Hay fever : Curryer<sup>2</sup> and others have stated that with the use of steroid hormones the relief from hay fever has been greater than what was previously achieved with hyposensitisation with ragweed extract or with the use of antihistamine drugs. The relief was however, largely confined to the period while cortisone was being administered.

Idiopathic (lethal) granuloma of middle line facial tissue : Cases are being reported with increasing frequency. If the dosage is based on findings of Schick and his co-workers in the treatment of periarteritis nodosa, with an initial dose of 300 mg of cortisone followed by 100 mg per 24 hours in divided doses, given every six hours and continued for a minimal period of six weeks, effective and rapid results may be expected.

In conclusion the use of cortisone and ACTH in the treatment of the diseases of E. N. T., may still be considered to be in the stage of clinical evaluation. With the exception of idiopathic granuloma other conditions described can be treated with reasonable success in most instances by other surgical and/or medical measures. It will therefore be well if the otolaryngologist would delay a little the use of these steroid hormones. For idiopathic granuloma these hormones offer the only hope of saving the patient's life. Corticosteroids have also been used to keep down granulations after certain laryngeal operations, as also to avoid fibrosis in a fresh case of oesophageal stricture. It is believed that these hormones are of some value in the treatment of early cases of Bell's palsy by lessening the oedema of the facial nerve.

Antihistamine drugs: These drugs only relieve symptoms; they have no curative value. Over 35 commercial preparations are on the market and it is not possible to choose any single drug as the best. Response varies with individuals ; the practitioner should familiarise himself with a few and prescribe in accordance with his particular requirements ; their sedative action varies from mild to severe. When prescribing these for a patient for the first time, the patient should be warned that there may be drowsiness and disorientation. When one drug fails to give the expected response, another may be tried. Birch<sup>12</sup> states that Antazoline is the least toxic, but at the same time the weakest. Diphenhydramine is undoubtedly the most sedative and so should be avoided for day time use, but is very useful at night in case a sedative action is desired. Promethazine is the longest acting (upto 24 hours). Chlorcyclizine is the longest acting antihistamine. Phenidamine is peculiar in that its side effect is excitation rather than sedation. Chlorpheniramine is the newest antihistaminic drug and is very rapid in action in a small dose".

Of the antibiotic ear drops one uses those of Aureomycin, Terramycin, or Chloromycetin. But these are expensive. Effective and moderately cheap preparations have been put up by

## Eclampsia

pharmaceutical laboratories. Scott Stevenson<sup>10</sup> states that a drop of water renders glycerine and carbolic ear drops caustic, therefore, he uses Auralgin. Ogilvie Reid<sup>6</sup> uses Chronalgin in chronic otitis media.

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## ECLAMPSIA

K. Bhasker Rao

Vigilant antenatal care and good diet in an educated population reduces the risk of eclampsia. These conditions have helped to reduce the incidence of eclampsia from one in 400 in 1947 to one in 5000 over the past five years in Sydney<sup>1</sup>. In Aberdeen, Nelson<sup>2</sup> reported 69 cases of eclampsia for 16 years in 12,908 primigravidae with only one maternal death. But in Madras for 13 years (1938-1950), 1151 cases of eclampsia were reported by Menon<sup>3</sup> with an average mortality of 15 per cent.

Management of eclampsia is still conservative on the lines suggested by Straganoff with sedatives and anticonvulsants as the aetiology is still unknown. Bromethol was tried in 130 eclampsies by Madhavan and Rao<sup>4</sup> with a maternal mortality of 5.4 per cent and gross foetal mortality of 11.2 per cent. In 1955, Mitra<sup>5</sup> and in 1956 Menon<sup>6</sup> used chlorpromazine in eclampsia. In the larger series reported by the latter 78 cases were treated with a foetal mortality of 11.2 per cent and three maternal deaths. This is a useful sedative, anticonvulsant and hypothermic drug. Till recently, the only indication for caesarean section in eclampsia used to be contracted pelvis. Menon on an analysis of 1151 eclampsia cases found 174 deaths, 145 of these in antepartum patients. He also found that the longer the interval between fits and the delivery the greater is the mortality. So in a series of 105 cases (75 per cent of whom were ante- and intrapartum eclampsia) he did lower segment caesarean sections under local anaesthesia in 25 patients. Only in 6 of these, fits recurred but were mild; he lost only one patient in the caesarean series. He concludes that in severe antepartum eclampsia where the cervix is closed and uneffaced and the presenting part is unengaged caesarean section should be done early when conservative therapy fails. This definitely reduces the mortality in this group of cases. But when the patients are in labour or where the cervix is ripe and the presenting part is engaged, artificial rupture of membranes is still the treatment of choice.

A rare complication seen following severe and prolonged eclamptic convulsions is described by Burnett<sup>7</sup> in 3 patients where they recovered from eclampsia, only to lead a vegetative existence for a variable period (3 weeks to 6 years) unable to talk or recognise their relations and displaying an absolute lack of emotions though they could take feeds or walk about. Autopsy in these cases showed cerebral softening or atrophy. It is suggested that this is a type of hypertensive encephalopathy induced by vasospasm in eclampsia.

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## ELECTRICAL CONVULSIVE TREATMENT

N. S. Vahia

Numerous attempts have been made to understand the mode of action of this line of treatment, but so far the results of these investigations have not been able to establish the exact mode of its action.

**Indications:** The need for electrical convulsive therapy has recently decreased because of the advances in the field of chemotherapy. Some of the major indications for this treatment were acute manic excitement and acute schizophrenic reaction following delivery, or any acute mental strain. For these conditions, tranquillizers in sufficiently large doses are so useful that quite often the electrical convulsive treatment is not necessary. This treatment, therefore, is used only in those cases that do not show any significant response to drugs. In depressive psychosis (reactive, involutional or senile) however, the tranquillizers are not very effective and therefore for this kind of mental illness, electrical convulsive therapy is still the treatment of choice. To a less extent it is useful in schizophrenia. It need not be stated that any physical therapy is meant for the relief of symptoms and the factors responsible for the mental illness have to be attended to when the patient is more amenable to psychotherapy.

**Contra-indications:** Just as the indications for this treatment have become less, the contra-indications have also decreased. Because of the modification in the technique of the therapy, electrical convulsive treatment has been given quite satisfactorily even in cases with organic diseases of the central nervous system (Shapiro<sup>7</sup>) and in advanced pregnancy without any harm (Smith<sup>6</sup>). Patients with bone diseases or recent fractures or dislocations can also be treated well. Elderly people can also stand the treatment well, and although it is used less often, the risk associated is minimal.

**Technique:** There were two major difficulties associated with the treatment: (1) Fear of the treatment and (2) the risk of complications like fracture, dislocation or cardiac strain.

To counteract a patient's fear of the treatment, barbiturates or tranquillizers are advised, but Kalinowsky<sup>4</sup> has warned against the use of premedication with electrical convulsive treatment because of the risk of complications, particularly the risk of prolongation of apnoeic period. Reserpine, one of the frequently used tranquillizers, has been associated with mortality or near mortality, when used with this treatment. Short-acting barbiturates are considered to be more helpful to decrease the chances of respiratory complications.

As complications associated with this treatment are due to the severity of convulsions, one method is to give electrical current in gradually increasing dosage over a period of few seconds and maintaining the tonic stage of convulsion for a longer period, to minimize the duration of clonic stage and thus decrease the chances of complications ('glissando' effect). It is considered that the incidence of complications has been much reduced by this technique (Idris<sup>2</sup>).

Most commonly used technique, however, is the use of a suitable muscle relaxant like succinyl choline with electrical treatment. By relaxing the musculature, it minimizes the risk of complications, like fractures, dislocations, cardiac strain, etc. The action of this drug lasts for only a few minutes. It has two drawbacks—(a) it causes painful twitchings when given in larger doses, (b) it stops respiration for sometime. To counteract these undesirable effects, pentothal is given intravenously prior to the administration of succinyl choline, so that the patient does not experience the painful twitchings and artificial respiration is maintained during the time of apnoea till normal respiration begins. The dosage of pentothal varies from 0.25 to 0.5 g and the dosage of succinyl choline 10 to 60 mg depending upon the body weight.

One of the common techniques used is as follows: the patient, after overnight starvation, is given atropine injection 1/100 gr intramuscularly prior to the electrical treatment. A 2.5 per cent solution of sodium pentothal is injected intravenously till the patient sleeps. This is followed by the injection of succinyl choline about 40 mg depending upon his age, the height, body weight and the physical condition. After cessation of fasciculation that follows succinyl choline injection, the patient's lungs are inflated with pure oxygen, before the actual application of the electrical current. The dose of the current is modified till the patient gets minimum convulsive seizures as noticed by the movements of the eyelids, the jaw and the extremities. This is followed by artificial respiration till the patient's own respiration begins (Steven<sup>8</sup>).

In actual practice, however, sodium pentothal and succinyl choline administration necessarily require the co-operation of an anaesthetist and a psychiatrist. Some workers believe that the need for an anaesthetist for pentothal and succinyl choline administration makes the treatment

## Electrocardiographic Changes in Pneumoperitoneum, Pneumothorax and Phrenic Crush

rather cumbersome. On theoretical grounds there is potentially greater risk of liver damage because of combination of pentothal and succinyl choline. They have therefore used succinyl choline alone (without pentothal) in a smaller dosage (Impastato<sup>3</sup>, Edward and Listwan<sup>1</sup> and Thomson<sup>9</sup>). The advantages of this modification are that it is simpler because an anaesthetist is not required and it is quite safe on account of a smaller dosage of succinyl choline being used. There is some difference of opinion regarding the advisability of using Impastato's technique on the ground that pentothal does not significantly increase the risk of liver damage but produces uncertainty in the mind of the therapist regarding the exact time of administration of electrical convulsive treatment and sometimes produces fear reaction in the patient because of the painful twitchings. Because of the fear of undesirable side effects, a psychiatrist might not use sufficiently large dose of succinyl choline to produce proper muscle relaxation (Marshall<sup>5</sup>).

Thus, with the improvement in the drug therapy, particularly the tranquillizers, the indications for this treatment have significantly become less. At the same time, in the hands of an experienced psychiatrist, the value of this treatment has increased, because many of the complications and hazards, not to mention the fear of treatment have been minimized. Hence, when indicated it can be used with much greater confidence by the therapist.

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## ELECTROCARDIOGRAPHIC CHANGES IN PNEUMOPERITONEUM, PNEUMOTHORAX AND PHRENIC CRUSH O. T. Samani

Earlier studies of E. C. G. patterns in pneumothorax<sup>1</sup> showed significant E. C. G. differences between those from right therapeutic pneumothorax and left one. In right sided pneumothorax, main changes were : tendency to right axis deviation, depression of QRS in Lead I, and depression of P wave in the limb leads. There was no T inversion. In left sided pneumothorax, the changes were : lower voltage of QRS, and flattening of T waves in Lead I, a change in contour of QRS complexes with definite T inversion in chest leads.

Evans and Black<sup>2</sup> reported 10 tuberculous patients with pneumoperitoneum with no evidence of heart disease. The E.C.G. changes comprised of abnormal Q waves in the standard or unipolar limb leads or the oesophageal leads; in each of the 10 cases abnormally large Q waves, usually associated with abnormal T waves, were obtained in oesophageal leads at ventricular levels. The position of the heart, especially forward displacement, rather than interposition of air between the electrode and the heart appeared to be a factor in the production of the consistently abnormal oesophageal Q waves. Assumption of the upright position generally caused an increase in the amplitude of the oesophageal Q and R waves with a decrease in the Q/R ratio; the T waves decreased in amplitude or became more deeply inverted as the author remarks.

Shreenivasan<sup>3</sup> from Singapore has reported E. C. G. changes in following types of cases:

(i) Pneumoperitoneum .. .. .	38 cases
(ii) Pneumoperitoneum and right phrenic crush .. .. .	16 "
(iii) Right phrenic crush .. .. .	15 "
(iv) Right-sided artificial pneumothorax .. .. .	10 "
(v) Left-sided artificial pneumothorax .. .. .	10 "
(vi) Pneumoperitoneum and left phrenic crush .. .. .	6 "
(vii) Left phrenic crush .. .. .	5 "
Total .. .. .	<u>100</u> "

An E.C.G was taken before and after these procedures in supine position with one pillow under the head. There were no significant changes in the P wave, PR interval, QT ratio, ST segment, and the T wave. Main changes were in the QRS complex.

Mechanical principles governing the movements of the heart in 3 planes are discussed by the author in detail, and E.C.G. changes are explained on that basis.

Following changes are described:

1. *Pneumoperitoneum* produced an increase in height of R in L 1 and aVL (due to shift to the left), increased R in  $V_2$ ,  $V_3$ ,  $V_4$  (due to counter clockwise rotation), decreased R in aVF and L 2, (due to interposition of air between the heart and the electrode).
2. *Pneumoperitoneum and right phrenic crush* produced increased R in L 1,  $V_2$  and  $V_4$  and decreased R in L 2, L 3, and aVF [due to causes given in (1) above].
3. *Right phrenic crush* produced decreased R in  $V_3$  and  $V_4$  and increased depth of S in  $V_2$  (due to clockwise rotation).
4. *Right-sided artificial pneumothorax* produced increased R in  $V_4$ ,  $V_5$  (due to counter clockwise rotation).
5. *Left-sided artificial pneumothorax* produced decreased R in L 1,  $V_4$  and  $V_6$  (due to shift to the right and clockwise rotation or low voltage due to the interposition of air between the heart and the electrode).
6. *Pneumoperitoneum and left phrenic crush* produced increased R in L 1 and aVL (due to shift to the left); and increased R in  $V_2$ ,  $V_3$  and  $V_4$  and decreased S in  $V_1$  (due to counter clockwise rotation).
7. *Left phrenic crush* produced increased R in Lead I (due to shift to the left), and decreased R in  $V_4$  and  $V_6$  (due to interposition of air between the heart and the electrode).

The author has also reviewed previous work on the subject.

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## ELECTROCARDIOGRAPHY

V. V. Shah and B. R. Patel

It is proposed to review here some of the recent advances in electrocardiography in the last few years. Limited space permits discussion of only a few of the important advances and their clinical significance.

This review is therefore, limited to a discussion of :

1. Electrocardiographic patterns in enlargement of the various chambers of the heart
2. The significance of electrocardiogram in congenital heart disease
3. Significance of QS pattern in myocardial infarction
4. Disappearance of Q wave following myocardial infarction
5. False patterns of myocardial infarction
6. Significance of the electrocardiogram in electrolyte disturbances
7. The value of oesophageal leads
8. The value of additional leads
9. ST-T segment changes.

**Electrocardiographic Patterns in Various Chamber Enlargements.**—A new concept of ventricular hypertrophy is promoted by the Mexican School of Cardiology, particularly by Cabrera<sup>2</sup>. Cabrera and his associates have proposed an electrocardiographic differentiation between increased flow work (diastolic overloading) and increased pressure work (systolic overloading) of the ventricles.

Systolic overloading of the right ventricle (e.g. pulmonary stenosis) is characterized by tall R waves with late changes in the ST-T segment and T waves in the right precordial leads. Diastolic overloading of the right ventricle (e.g. atrial septal defect) manifests itself by patterns of right bundle branch block. Systolic overloading of the left ventricle (e.g. aortic stenosis)

## Electrocardiography

is characterized by negative T waves with negative RS-T displacements, showing upward convexity in left precordial leads. Diastolic overloading of the left ventricle (e.g. patent ductus arteriosus) is characterized by high voltage and the presence of elevated RS-T segment with a peaked T wave in left precordial leads.

Zukerman<sup>15</sup> and his associates have studied the electrocardiographic patterns of auricular enlargement. In general, a tall and sharp P wave suggests right auricular enlargement, while a broad P wave (duration more than 0.11 to 0.12 sec.) which may be bifid, rounded or flat-topped, suggests enlargement of the left auricle. When both features are present, enlargement of both the auricles is likely to be present.

Penaloza<sup>9</sup> and others in a recent study of pure or complicated pulmonary stenosis have found that the sharp and tall P wave is very often present in cases with a lowered oxygen saturation of the arterial blood. There appears to be an inverse relationship between the degree of saturation and the changes in the P wave. The sharp and tall P wave was also found, but less frequently, when there was an elevation of the right ventricular systolic pressure usually above 130 mm Hg. The most striking changes in the P waves were noted in those cases with both, low oxygen saturation and high systolic pressure in this chamber.

**Electrocardiogram in Congenital Heart Disease.**—Electrocardiographic study is a valuable aid in the diagnosis of congenital heart disease. This study has become increasingly important as surgery is offering more and more help everyday for the treatment of these anomalies.

*Atrial Septal Defect:* Limon<sup>6</sup> reports an incidence of 80 per cent in his series having incomplete right bundle branch block and 6 per cent having complete right bundle branch block. A number of cases having pulmonary hypertension shows systolic overloading type of pattern of right ventricular hypertrophy, characterized by tall R waves in the right precordial leads. He further reports an incidence of 25 per cent of cases having a prolonged P-R interval and states that P wave may show increased voltage and duration, and may be peaked. The electrocardiogram in atrial septal defect, having ostium primum type of defect may show left axis deviation in standard leads, and patterns of right ventricular hypertrophy or bilateral ventricular hypertrophy in the chest leads.

*Ventricular Septal Defect:* Electrocardiographic changes depend essentially on the pressure in the cavity of the right ventricle. If the defect is small, the electrocardiogram may be normal or may show a pattern of left ventricular hypertrophy. With a large defect, the electrocardiogram may show evidence of enlargement of both the ventricles. If the pressure in the right ventricle is still high, the electrocardiogram may show the pattern of right ventricular hypertrophy, at the same time masking the pattern of the left ventricular hypertrophy. Sodi-Pallares and Marsico<sup>12</sup> report that 62 per cent of the cases showed signs of left ventricular hypertrophy and 56 per cent of the cases showed evidence of combined hypertrophy of both the ventricles. Twenty-two per cent of the cases showed an incomplete or complete right bundle branch block, without any evidence of ventricular hypertrophy.

Deep Q waves in V<sub>5</sub> and V<sub>6</sub> suggesting septal hypertrophy and Katz-Wachte<sup>1</sup> sign characterized by high isodiphasic QRS complexes in V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub>, are frequently present in ventricular septal defect.

P waves may be abnormal. They may show either a left auricular or a right auricular enlargement, or may show evidence of enlargement of both atria. Marsico<sup>7</sup> and associates reported that 70 per cent of the cases showed increased duration of the P wave. Left auricular enlargement was found in 30 per cent and right auricular enlargement was present in 10 per cent. Twelve per cent of the cases may show a first degree of A-V block.

*Patent Ductus Arteriosus:* Electrocardiographic changes depend on whether the patent ductus arteriosus is with or without pulmonary hypertension. Thus, the electrocardiogram may be within normal limits when the duct is small. If the duct is large, the electrocardiogram may show the pattern of left ventricular hypertrophy. When there is associated pulmonary hypertension, the electrocardiogram may show patterns of biventricular hypertrophy. If the pulmonary hypertension is very marked, the electrocardiogram may only show a pattern of right ventricular hypertrophy masking the pattern of the left ventricular hypertrophy.

*Pulmonary Stenosis:* Electrocardiographic changes depend upon the degree of pulmonary stenosis. It may vary from normal to one showing a systolic overloading pattern of the right

ventricle, characterized by tall waves with depressed RS-T segment and inverted T waves in the right precordial leads. Tall and peaked P waves may be present.

In a series of 170 cases analysed by Paul Wood,<sup>8</sup> 38 per cent had mild stenosis and did not reveal any abnormal electrocardiographic changes. Twenty-five per cent had moderate stenosis with evidence of right ventricular hypertrophy and among these about 40 per cent showed a sharp P wave. Thirty-seven per cent had a severe pulmonary stenosis where the electrocardiogram invariably showed a marked right ventricular hypertrophy. Tall and sharp P waves accompanied the QRS-T changes.

*Fallot's Tetralogy and Triology* : In contrast to the lone pulmonary stenosis, the electrocardiographi: changes of right ventricular hypertrophy in Fallot's tetralogy are relatively less pronounced because of the associated ventricular septal defect and the dextroposition of the aorta. Paul Wood<sup>8</sup> reports a frequency of 42 per cent of normal P wave in Fallot's tetralogy. He lays emphasis on this frequency of the normal P wave in contrast to the tall and sharp P waves occurring in Fallot's triology.

*Eisenmenger's Complex* : In practically all instances, the electrocardiogram shows right ventricular hypertrophy alone or in combination with left ventricular hypertrophy. Twenty-five per cent of the cases may show evidence of right bundle branch block. Most of the cases show wide, somewhat tall P waves in the standard limb leads, suggesting combined atrial hypertrophy. Complete heart block is rare. First or second degree of A-V block is present in 10 per cent of cases.

*Transposition of the Great Vessels* : Since the right ventricle has to work against increased systemic pressure, the electrocardiogram shows a pattern of the systolic overloading type of right ventricular hypertrophy. Since the blood flow through the left ventricle may also be increased, signs of left ventricular hypertrophy are sometimes present as well. Fifty per cent of the cases may show sharp and tall P waves.

*Tricuspid Atresia* : The underdevelopment of the right ventricle and dilatation and hypertrophy of the left ventricle and the two atria, particularly the right atrium, cause characteristic changes in the electrocardiogram.

Brink and Neill<sup>1</sup> analysed the electrocardiographic changes in 81 cases of tricuspid atresia. They found 86 per cent had left axis deviation and 83 per cent had left ventricular preponderance in the precordial leads.

The P wave in tricuspid atresia is invariably abnormal. Most commonly it shows a pattern of tall and sharp P wave. There may be an evidence of biatrial enlargement.

*Ebstein's Syndrome* : Most of the cases show incomplete or complete right bundle branch block. The voltage may be low. Complexes may be a little bizarre with an increased duration. Some cases may only show a QR pattern in the right or all the precordial leads due to a massive enlargement of the right auricle. Others may show the pattern of Wolff-Parkinson-White syndrome. Arrhythmias are common in Ebstein's anomaly.

*Single Ventricle* : The electrocardiogram may reveal a variety of patterns. Theoretically, the presence of a single pattern in all the unipolar chest leads should be expected but this is found only in few patients. Some cases may, however, show a complete right bundle branch block whereas others, an incomplete left bundle branch block. In some cases there may be a right axis deviation, in others, left axis deviation. Some cases may show either a pattern of the right or the left ventricular hypertrophy. Peaked P waves in the limb leads have also been described.

*Coarctation of Aorta* : Paul Wood<sup>8</sup> reported that 46 per cent of cases of coarctation had a normal electrocardiogram. Twenty-three per cent had slight left ventricular preponderance and 20 per cent had marked left ventricular hypertrophy. Seventy-five per cent of the cases which showed marked left ventricular hypertrophy were associated with aortic stenosis. Thus only 5 per cent of the uncomplicated cases showed electrocardiographic evidence of serious left ventricular strain. Eleven per cent of the cases showed evidence of right bundle branch block. Ziegler<sup>14</sup> suggests that a right bundle branch block might represent a residual change from right ventricular preponderance in utero, at a time when the foetal ductus joined the aorta above the stricture.

*Anomalous Origin of the Left Coronary Artery from the Pulmonary Trunk* : The electrocardiogram shows negative, peaked T waves in the left precordial leads. Some cases may



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show deep Q waves with positive displacement of the RS-T segments in the precordial leads, AVL and in lead I, simulating an anterior myocardial infarct.

**Significance of QS Pattern in Myocardial Infarction.**—Recently Prinzmetal<sup>10</sup> and his associates have shown that the QS pattern does not invariably mean that the entire thickness of the wall is infarcted. This newer concept is based on the fact that the ventricular wall, from the standpoint of changes in the electrical potentials, may be considered to be consisting of two layers—an inner two-thirds and an outer one-third. Conduction of the inner two-thirds is by way of penetrating fibres of the Purkinje network and is so rapid as to be almost instantaneous in all this portion of the ventricular muscle. In the outer third, conduction takes place by way of muscle fibres only. The conduction rate is therefore, relatively slow. It has been shown that the QS pattern will be registered even though the infarct may be limited to the outer third of the ventricular wall.

**Disappearance of Q Wave Following Myocardial Infarction.**—Patients having cardiac pain due to coronary disease with cardiographic changes present in ST-T segments only, not uncommonly show disappearance of inversion of T wave in few or all leads, when followed up with serial electrocardiograms. Cardiograms showing myocardial infarcts with Q waves show recovery of ST-T segments with even upright T waves, but abnormal Q waves usually persist. Few cases have been reported showing disappearance of abnormal Q waves in posterior myocardial infarcts (Bohning and Katz)<sup>16</sup>. Shah (1956)<sup>18</sup> reported for the first time a case of antero-septal myocardial infarct with disappearance of Q wave and reappearance of R wave with complete cardiographic recovery. This is rare, and lately Pappas (1958)<sup>17</sup> has reported nine cases of antero-septal infarcts with disappearance of Q waves and reappearance of R waves.

More complete the cardiographic recovery, better the prognosis. The return of the cardiogram to normal is due to the shrinkage of the healed area in a part of the myocardium not electrically detectable. A further factor may be the development of an efficient collateral circulation.

**False Patterns of Myocardial Infarction.**—A few cardiac conditions present electrocardiographic patterns that may easily be mistaken for those of myocardial infarction. We are well conversant with some of these patterns. But recently Guzman and Sodi-Pallares<sup>3</sup> have summarized these conditions into four different groups.

1. *False Patterns of Antero-septal Infarct*: QR or qR patterns in the right precordial leads may appear when there is great dilatation of the right auricle. Certain cases of acute cor pulmonale are likely to be misleading because in addition to QR or qR patterns in the right precordial leads, they often show positive RS-T displacement with negative T waves in these leads. This may lead to the diagnosis of a non-existent antero-septal infarct.

In left bundle branch block and in left ventricular hypertrophy the QS pattern may appear with positive RS-T displacements in the right precordial leads in the absence of an antero-septal infarct.

2. *False Pattern of Lateral Infarct*: QS tracing may appear in lead I and AVL in cases of marked left auricular dilatation.

3. *False Patterns of Extensive Anterior Infarct*: Chronic cor pulmonale may show QS or W shaped complexes in leads I, AVL and all precordial leads.

4. *False Patterns of Posterior Myocardial Infarct*: In Wolff-Parkinson-White syndrome QS complexes appear in leads II, III, and AVF and such findings may be mistaken for posterior myocardial infarct.

**Electrocardiographic Changes in Electrolyte Disturbances.**—With the better understanding of the importance of the electrolytic balance in health and disease, the study of electrocardiographic changes in various disorders of electrolyte balance have assumed a special significance. The electrocardiographic changes in the following conditions are considered here.

*Hypopotassæmia*: This is frequently encountered in congestive cardiac failure treated with mercurial diuretics, aldosteronism, kidney disease, diabetic acidosis, cortisone therapy, etc. There is a lowering and broadening of the T wave with prolongation of the Q-T interval. There may be a low and broad T wave with a double summit due to superimposition of the U wave on the T wave. The RS-T segment may be depressed with a downward T wave. A prolonged P-R interval may occur in association with any of the above patterns.

*Hyperpotassæmia*: This is met with in uraemia and Addison's disease. The T wave may become tall and peaked with a narrow base. The P waves may disappear or wander in and out

of the QRS complexes. The QRS complex may become widened and may show bizarre patterns. The electrocardiogram may show biphasic deflection caused by fusion of the QRS complex with the RS-T segment and the T wave. At a still later stage, ventricular fibrillation or complete cardiac standstill may occur. With the onset of the wide, aberrant QRS complexes and the loss of the P wave, an idioventricular rhythm may develop.

**Hypocalcaemia :** This is present in hypoparathyroidism and may occur after thyroidectomy if the parathyroid glands are injured. Here the RS-T segment becomes lengthened and the QT interval becomes prolonged. However the T wave remains more or less normal in its shape and size.

**Hypercalcaemia :** This occurs in hyperparathyroidism and sometimes with excessive vitamin D therapy. Here the Q-T interval is shortened and a normal T follows. The shortened Q-T interval is due to a shortening of the RS-T segment.

**The Value of Oesophageal Leads.**—The oesophageal leads have recently been more extensively used in electrocardiography by various investigators. They show a better configuration of the auricular complex and the auricular T waves. Since the oesophageal leads are anatomically closely related to the posterior wall of the left ventricle, their study has helped in the diagnosis of posterior myocardial infarction, particularly when the infarct is small. Their study has also helped in the diagnosis of various auricular arrhythmias which are obscured in the precordial and the limb leads.

**The Value of Additional Leads.**—It has been shown by Wilson<sup>13</sup> and associates, Klein and Myers<sup>4</sup> and others that infarction of the middle and the upper portion of the lateral wall of the left ventricle may be missed in the usual precordial leads, but may be recorded by leads taken in positions V<sub>3</sub>, V<sub>4</sub>, V<sub>5</sub> and V<sub>6</sub>, in the third left intercostal space.

Lambert<sup>5</sup> has shown that the lead V<sub>1</sub> can explore the anterior wall of the left ventricle and the interventricular septum. This lead shows direct infarct patterns in nearly all the anterior, antero-septal and posteroseptal infarcts.

The leads V<sub>0</sub> and V<sub>EO</sub> give information relative to the posterior and postero-lateral walls of the left ventricle. They show infarct patterns in a plain posterior infarction.

The leads V<sub>3</sub>R and V<sub>4</sub>R are useful in the diagnosis of right ventricular hypertrophy, right bundle branch block and of an antero-septal infarct.

**ST-T Segment Changes.**—Without any demonstrable organic heart disease, mild ST-T segment changes are quite frequently met with. It is advisable in such cases to evaluate clinical data as a whole and may be of help in the assessment of such changes. Extracardiac conditions like anaemia, malnutrition, administration of certain drugs like digitalis, quinidine, myxoedema, electrolyte imbalance etc. may give rise to such changes. Such changes have also been quite frequently met with in emotionally unstable individuals and are possibly due to imbalance of the autonomic nervous system.

Shah and Kunjannam<sup>11</sup> have discussed on the use of the term “strain” in clinical electrocardiography and consider it misleading and unhelpful in the understanding of the underlying pathology responsible for the basic condition. They have reported ST-T segment changes without high voltage in patients having definite left ventricular enlargement. Such cases were usually complicated by causes like coronary disease, congestive cardiac failure, generalised oedema, emphysema, anaemia, etc. They, therefore, advise to look for some associated disease in patients having left ventricular enlargement if the voltage is not high, however typical ST-T segments may appear.

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## Encephalitis in Children

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## ENCEPHALITIS IN CHILDREN

J. B. Mehta

Encephalitis in children continues to be a problem as the aetiology is varied and even where one considers the infective, epidemic variety, no two epidemics are alike and the causative agent often remains obscure. In India a number of epidemics have been described in the past few years. "Jamshedpur fever" or the "Mystery disease" between June-October 1954 was a very severe epidemic that spread throughout northern India.<sup>3,6,7</sup> The fatality rate in Jamshedpur was 13.5 per cent but in other places it was higher<sup>4,7</sup>.

In South India similar epidemics of encephalitis have been recorded recently. The epidemic between September to December 1955 was extensively studied<sup>5,9</sup> and further studies have extended to all cases seen till December 1956<sup>8</sup>.

In the influenza epidemic of April to August 1957 the incidence of encephalitis was small. In the series from Bombay<sup>10</sup> signs of involvement of the central nervous system were only 8.1 per cent. In this epidemic encephalitis and respiratory complications were the main causes of death. Full reports of this epidemic are not yet published.

Clinically Jamshedpur fever was of very sudden onset with vomiting, hyperpyrexia, twitchings, convulsions, delirium, neck rigidity and a positive Kernig's sign. Blood leucocyte count was raised, blood sugar reduced markedly, C. S. F. was normal except for low sugar. Death occurred within 48 hours. Less severe types recovered<sup>3,6,7</sup>.

The South Indian encephalitis had a prodromal stage of 1 to 4 days of fever with chill, rigor, headache and malaise. In the encephalitic stage the fever continued and convulsions, coma, neck rigidity, focal signs of paralysis, choreoathetosis (50 per cent of cases) appeared. Blood leucocytosis was present. C. S. F. showed pleocytosis with slightly raised protein and normal or raised sugar. The disease course varied from 6 to 46 days<sup>5,9</sup>.

Hence the two epidemics were different clinically, Jamshedpur fever being highly explosive with a high mortality rate. The South Indian variety was more like the accepted course of encephalitis with a lower mortality rate, but with (50 per cent) focal neurological lesions.

No virus could be isolated in either epidemic. Cocksackie virus A and the Orphan virus of Melnick were isolated from some cases but no definite correlation could be found. So much so that the Medical Research Council of India, Virus Centre, Poona, has suggested<sup>1</sup> that at least the Jamshedpur fever may not be of viral origin and may be of the Japanese Ekiri fever type in which the causative organism was finally established to be the B Shiga, the "encephalitic" manifestations being due to biochemical changes, e.g. hypocalcaemia and hypoglycaemia. They stress the need for searching for other organisms than a virus for "encephalitis epidemics". The South Indian epidemic was said to be due to Japanese B type encephalitic virus<sup>5,8,9</sup>. This assumption was based on serological findings in the earlier cases. No virus was isolated. In view of the relation of Japanese B encephalitis virus being implicated in this epidemic an article by Gieraths and Yokoto is worth consulting. They also seem to have found para-aminonaphthalene sulphonamide (PANS 610) to be an effective, though toxic chemotherapeutic agent ; vaccines for immunisation against this virus are available in Japan.

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## ENDOCRINE GLANDS, PHYSIOLOGY OF

R. K. Pal

**The Adrenals.**—Lobhan (1957)<sup>13</sup> produced an increased development of the zona reticularis of the cortex of the sexually immature male cat by an alteration in balance of the sex hormones by direct action by the ICSH of anterior pituitary. Burns, Hale and Hutchison (1957)<sup>14</sup> showed that ACTH caused an appreciable increase in the size of the nuclei without effecting the total amount (extinction X area) of the deoxyribonucleic acid (DNA) present in each nucleus, which was also corroborated by biochemical methods. Cater and Stack Dunne (1955)<sup>5</sup> showed that the mitotic activity of the adrenal cortex of rat begins to fall 2 to 3 days after hypophysectomy, is low by the 8th day, very low at 67 days and the zonal distribution of mitosis becomes more central within 32 to 72 hours. The percentage of mitosis in anaphase and metaphase stages increases from 12-21 to 48 hours and remains always higher in hypophysectomised animals. The same workers (1955a)<sup>6</sup> again showed that 1 to 5 mg of the growth promoting hormone, injected in a single dose (I. P.) into rats hypophysectomized 10-21 days previously, increases the number of mitosis in the adrenal cortex in 4-8 hours. When half the initial dose is repeated at 8-hourly intervals the mitotic response does not increase at once after the initial peak and is low and variable at 12 and 16 but is high at 24 hours.

Marthe Vogt (1955)<sup>21</sup> injected into rats hexoestrol (0.3-0.5 mg/kg daily for 2 to 11 days) and by estimating the cortical secretion released into the adrenal venous blood colorimetrically showed that the lipide-depleted glands secreted much less corticosterone than normal glands, for which as a substitute no other corticosteroid compound was found. The fact that corticosterone secretion was normal on discontinuing hexoestrol, proved that oestrogens inhibited the normal function of the cortex in rats. The same worker again (1955a)<sup>22</sup> postulated that the hypertrophy of the adrenals after prolonged administration of hexoestrol is due to a release of ACTH by the low level of the circulating corticosterone. The lipide-depleted adrenal of the rat given hexoestrol responds to stress by a fall in its ascorbic acid concentration, while that of rabbits was not inhibited by hexoestrol even with much higher doses.

Woods (1957)<sup>24</sup> has proved that no metabolic depletion of adrenal cortex occurs in Norway rats under conditions of stress (due to 2-4°C) for various periods up to 24 hours which usually produced depletion of ascorbic acid and sudanophilic lipide in the cortex of domesticated rats. ACTH however, resulted in depletion of these components but a larger dose is necessary for wild rats than for the domesticated ones. Symington and Davidson (1956)<sup>19</sup> have also recorded similar findings due to effects of ACTH and conditions of stress on the chemical composition of the human adrenal glands. Woods (1957a)<sup>25</sup> has again shown that although the adult Norway rats have adrenals about twice the size as in domesticated rats under normal conditions and following exposure to cold, the concentration of ascorbic acid is unchanged in both strains, in spite of the increase in weight in the stressed domesticated rats on continuous exposure to freezing temperature for 26 days although no such hyperactivity occurred in wild rats.

The study of cytochemistry of the regenerating adrenals after enucleation by Pellegrino and Torigliani (1957)<sup>15</sup> sometime between 15 to 90 days after the operation, revealed that the size of the average cell and contents per cell such as DNA, acid soluble phosphorus, ether, cholesterol, ascorbic acid etc. vary with changes in activity and the contents per cell although they increase slightly in the beginning of regeneration and decrease afterwards. Fatty acids on the contrary, after an initial decrease showed a marked increase later on. The enzyme constituents with the exception of acid and alkaline phosphatase (e.g., glucuronidase) also behave similarly during the first month of regeneration. As to RNA no variation in concentration was noticed in the regenerating tissue and RNA content per cell alters in parallel with the total nitrogen and DNA. Blaschko, Hagan and Welch (1956)<sup>2</sup> have shown that the cytoplasmic granules of the bottom layer which are rich in catecholamines are also rich in ATP while granules of the top layer which contain less amines are also poorer in ATP. The molar ratio, adrenaline : ATP calculated as a mean of the results was 6.7 for the bottom layer and 9.8 for the top layer (in 1.5 M-sucrose high speed centrifugation and sedimentation).

Aldosterone, the amorphous fraction of the adrenal extract has been isolated from the blood of systemic and adrenal veins and also from urine; it has also been crystallized recently. Its true nature has been determined and formula established; this is equivalent to that of corticosterone with an aldehyde substitute at 18 carbon atom and has been recognised as the chief hormone for regulation of K, Na, Cl and possibly Mg ions (Review by Renzi and Chart, 1955)<sup>17</sup>. The hormone has since been synthesized by Wettstein and Schmidlin (1955).

## Endocrine Glands, Physiology of

Rawat, Gupta and Roy (1957)<sup>16</sup> showed that in young male rats administration of thiourea for seven days did not produce any hypertrophy of thyroid and pituitary but there was a very marked increase in the weight and size of these glands on the 14th day. This indicated that the amount of preformed thyroxine stored in the thyroid was enough to meet body requirements for a week or so. Simultaneous administration of thyroxine or ACTH with thiourea did not allow any increase in the weight of the gland. It was also observed that stunted body growth in these hypothyroid rats was mainly due to decreased consumption of food which increased sharply and so the weight too, on withdrawal of the goitrogen.

**The Pituitary.**—Chaudhury and Sen (1957)<sup>7</sup> have shown that adrenal ascorbic acid depletion induced by adrenalectomy in rats cannot be inhibited by hydrocortisone and morphine. The site of this blocking effect is not the adrenal cortex as the same is also caused by ACTH indicating that ACTH secretion is blocked, the mechanism and site remaining unknown. But Briggs and Munson (1955)<sup>3</sup> also noticed that morphine caused adrenal ascorbic acid depletion in anaesthetized rats, which according to George and Way (1955)<sup>11</sup> is dependent on an intact pituitary.

Ovulation has been produced by Donovan and Harris (1956)<sup>10</sup> in the rabbit by injection of adrenaline or noradrenaline solutions into the hypothalamus or by adrenaline into the pituitary gland. When the solutions of the adrenergic drugs were neutralised before use the effectiveness of the injection was greatly diminished, which observation does not support the view that an adrenergic agent is concerned in the humoral transmission of stimuli from hypothalamus to the pituitary. Abrahams and Mary Pickford (1956)<sup>1</sup> have shown that injection of eserine sulphate or diisopropyl-fluorophosphate into supraoptic nuclei of chloralosed dogs caused an increase in the size of uterine contractions, which supports the view that oxytocic-like antidiuretic factor of the neuro-hypophysis can be released by cholinergic transmission to the supraoptic neurones.

Ross (1955)<sup>18</sup> has shown that alkaline extract of anterior pituitary used as a source of growth hormone, accelerates in rats the transfer of glucose across blood-aqueous barrier of the rabbit. Simultaneous administration of insulin causes no further increase in the rate of entry of glucose into the eye, which is not reduced by a large dose of insulin given concurrently with anterior pituitary extract, suggesting that the insulin-like effect of the growth-hormone is not due to liberation of insulin from the pancreas. Daniel and Prichard (1957)<sup>8</sup> made observations on necrosis of the anterior lobe after stalk section and various other methods, that the anterior lobe is supplied by hypophysial portal vessels in sheep; however according to Xuereb, Prichard and Daniel (1954)<sup>26</sup> and Daniel and Prichard (1956)<sup>9</sup> there is no such direct arterial supply in man and rat respectively.

On assaying the vasopressor, oxytocic and antidiuretic activities of dispersion of rat's pituitary in 0.25 M or 0.088 M sucrose before and after centrifugation at 19,000-22,000 revolutions at 0°, Ursula, Pardoe and Weatherall (1955)<sup>20</sup> were of opinion that the antidiuretic activity accompanied the pressor activity and some and possibly all the oxytocic and vasopressor material was present in cytoplasmic particles which behaved like mitochondria. Individually they probably do not contain the two factors together.

**The Parathyroids.**—Howard (1955)<sup>12</sup> in a Ciba Foundation symposium summarised, 'The chief function of the parathyroid hormone is to regulate the equilibrium (set up between the bone crystals and fluid into which they are bathed) at the interface between the crystal and the tissue fluid'. So the parathyroids regulate the living barrier between the bone salt and tissue fluid, which while supporting Collip's theory that parathyroids regulate the mobilisation of calcium from bones, does not go against Albright's hypothesis that parathormone regulates the reabsorption of phosphate by the renal tubules.

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**ENDOMETRIAL CANCER**—See CANCER, ENDOMETRIAL

**END-ORGAN DEAFNESS**—See DEAFNESS, END-ORGAN

## ENVIRONMENTAL HEALTH

A. K. Niyogi

**Water** : Great difficulty is experienced in sending water for bacteriological analysis to laboratories from towns and villages distantly situated as variations in bacterial contents begin to take place very early. Even ice packing can be effective to maintain the sample unchanged in bacterial content for only a short time.

Copper, zinc, distilled water and even de-ionised water can reduce the coliform bacillus count within 24 hours.

Hence the results reported by Shipe and Fields<sup>1</sup> are of special importance to all health workers specially those working in outlying districts. It is said that EDTA (tetra sodium salt of ethylene diamine tetra-acetic acid) was non-toxic to *E. coli* in  $10^{-2}$  to  $10^{-6}$  concentration in water. For 24 hours this chelating agent was of value in retaining the coliform index nearer the level existing at the time the sample was taken.

Chlorination of water with high level of residual chlorine of 0.8 ppm or so, always brings about complaints from the medical profession and the lay public in towns and villages. Muegge<sup>2</sup> investigated the physiological effects of heavily chlorinated drinking water and found that 5 ppm of residual chlorine in water used for a prolonged period by the U. S. Army did not give rise to any ill health among the men.

Different methods are being tried for disinfection of water as the present method of chlorination is not always satisfactory. Tredre<sup>3</sup> reports the use of silver ions (0.05 ppm) and a ten minute contact as a satisfactory method. Immersion of candle with silver impregnation or that of silver electrodes and a very weak current passing between them in the water are offered as the methods for this purpose.

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**EOSINOPHILIA IN FILARIASIS**—See FILARIASIS, EOSINOPHILIA IN

**EPILEPSY, PSYCHOMOTOR**—See TEMPORAL LOBE, FUNCTIONAL DIVISIONS OF ; PSYCHOMOTOR EPILEPSY

## EPILEPSY, TREATMENT OF

A. R. Govinda Rao

Modern drug therapy of epilepsy began nearly one hundred years ago, when bromide was first used by Sir Charles Locock, based on the premise that epilepsy was due to onanism and bromide elicited an anaphrodisiac effect. With the introduction of phenobarbital as an anti-convulsant by Hauptmann in 1912 and diphenylhydantoin (Dilantin) by Merritt and Putnam in 1937, interest in bromide therapy progressively decreased. Ever since tridione and mesantoin

## Epilepsy, Treatment of

were investigated in 1944, a series of additional drugs such as Mysoline, Gemonil, Phenurone and Diamox have been introduced in the therapeutics of epilepsy.

Many of the drugs are derivatives of urea and act as clinical suppressives. None is capable of curing the disease completely and hence present-day therapy is palliative rather than curative. Nevertheless it is possible to control seizures completely and make the life of an epileptic more tolerable by a systematic drug therapy supplemented with general hygienic measures and psychiatric care.

In a person who has a convulsive diathesis numerous trigger mechanisms exist like emotional disturbances, fever, gastro-intestinal upsets, excessive intake of fluids especially alcohol, constipation, frustration, emotional tensions and allergic episodes. Occasionally the number of seizures increases during some phase of the menstrual cycle. The state of boredom nurtured by the lack of occupation or recreation may increase the tendency to seizures. In many instances the institution of general hygienic measures and psychiatric care are more important than drug therapy in controlling seizures. Generally, seizures associated with evidence of other organic brain disease are more refractory to drug therapy than are the idiopathic type of seizures. Surgical procedures such as extirpation of discharging cortical foci should be considered only when medical management has failed and spells are of a focal nature.

The objectives of therapy are to control seizures completely and as long as possible. The patient must be given an opportunity to live a normal life as far as is feasible. The choice of the best possible drug or combination of drugs is sometimes difficult. It is made on the basis of clinical appraisal of the type of seizures as well as, on diagnostic data obtained by E.E.G. examination. Adjuvant metabolic measures such as ketogenic diet and water restriction are occasionally helpful.

A brief review of the important group of drugs at present available as antiepileptic agents, would focus light on the following :

*Grand mal*—Phenobarbital, diphenylhydantoin, mesantoin, metharbital, primidone (Mysoline).

*Petit mal*—Trimethadione, paramethadione, methyl phenyl succinimide (Milontin), diamox.

*Psychomotor epilepsy* — Phenurone (Phenacemide).

*Epilepsy with focal damage* — Phenaglycodol (Ultrane).

Phenobarbital (Luminal) was introduced by Hauptmann in 1912. The drug has definite advantages in that it is least toxic of all antiepileptics ; its action starts within an hour or two after ingestion ; it is of value in the control of status epilepticus and grand mal and can be used without the necessity of periodical physical and laboratory examinations. It is also inexpensive. Nearly 70 per cent of cases of grand mal, when properly treated, show improvement in respect of severity and frequency of seizures and mental and physical well-being. Since it produces drowsiness and some measure of central depression the drug is inferior to diphenylhydantoin.

If carefully regulated doses of phenobarbital are not successful in preventing convulsions in grand mal, drug combinations should be tried. In refractory cases a combination of phenobarbital with dilantin has a markedly superior effect to administration of either drug. If depression is severe, amphetamine and other centrally active preparations may be combined to obtain maximum benefit.

Although phenobarbital is quite effective in grand mal, it gives only partial, temporary or inconstant results in petit mal and is of doubtful benefit in psychomotor epilepsy.

Diphenylhydantoin (Dilantin) was introduced by Merritt and Putnam in 1938 as an anti-convulsant. Patients with grand mal seizures are markedly benefitted by the drug and psychomotor attacks are sometimes controlled. Dilantin offers the special advantage of possessing a specificity for the motor cortex and not affecting the sensory areas of the brain to any appreciable extent, and it becomes possible to treat epilepsy without producing dullness of perception, lethargy, and lassitude which so frequently accompany bromide and phenobarbital therapy.

In the treatment of grand mal several days are required to build up a satisfactory level of the drug activity in the brain. Thus a lag period is observed before any improvement is found in patients and if phenobarbital is suddenly withheld and Dilantin subsequently substituted, there is a possibility of precipitating frequency of seizures or even status epilepticus. In petit mal triad, dilantin is of little aid and may even increase the number and severity of seizures (Merritt and Putnam).

A number of toxic effects mainly referable to the central nervous system, the gastro-intestinal tract, the liver, the skin and bone marrow are met with. The unsightly hypertrophy of gums frequently seen in children may be avoided by the addition of large doses of ascorbic acid in diet.

Mesantoin has more sedative effect than dilantin and is often well tolerated by patients who cannot take the former drug. In grand mal and focal attacks Mesantoin occasionally provides better control of seizures in refractory cases than obtainable with phenobarbital or Dilantin (Kozol). Unfortunately, these advantages are offset by a higher incidence of skin rashes, blood dyscrasias and hepatic impairment (Abbott and Schwab).

Primidone (Mysoline) was synthesized by Bogue and Carrington in 1953. It is a congener of phenobarbital and has been used to advantage in patients with grand mal. It may control seizures when other agents have failed. Livingston and Peterson's study of 486 cases indicates that primidone is primarily of value in the treatment of grand mal and almost useless in petit mal or psychomotor seizures. Drowsiness was the most frequent side reaction observed. Neither haematologic disturbances nor irreversible toxic disturbances were encountered in any of their patients.

Metharbital (Gemonil) is one of the few barbiturates that exhibit the antiepileptic properties of phenobarbital. It has been found of value in certain cases of grand mal, pyknolepsy and seizures with mixed clinical picture. Apparently it is much more effective in seizures caused by organic brain disease than in idiopathic epilepsy (Perlstein). Toxicity is minimal after metharbital medication. Untoward responses occasionally observed include increased irritability, skin rash, dizziness, gastric distress and drowsiness.

Trimethadione (Tridione) was synthesized by Spielmann in 1944. Its anticonvulsant properties were recognised and investigated by Everett and Richards. It is highly specific in the treatment of petit mal (Richards and Perlstein). The drug is not only an anticonvulsant but is also an analgesic and compares with codeine in its ability to elevate the pain threshold. The drug is also effective in certain cases of behaviour disturbances in children, probably due to a sedative action. Toxic reactions are drowsiness, hemeralopia (Sloan and Gilger), dermatitis and blood dyscrasias (Davis and Lennox). Trimethadione is not indicated in patients with grand mal or in psychomotor seizures.

Paramethadione (Paradione) was first reported as clinically useful as an antiepileptic drug by Davis and Lennox (1949). It is a clear, colourless, oily liquid marketed in capsules containing 0.15 to 0.3 g for oral use. It is indicated only in petit mal triad, and the action is almost similar to tridione. Paradione is more sedative but the incidence of photophobia and skin rash is lower. Even blood dyscrasias are probably less frequent than with the use of trimethadione.

Methyl phenyl succinimide (Milontin)—its anti-convulsant properties were first studied by Chen (1951). This drug has been found to be particularly effective in petit mal (Zimmerman). About a third of the cases are completely cured and another third considerably improved. Toxic symptoms are drowsiness, skin rashes and gastro-intestinal upset.

Phenurone (Phenacemide) was synthesized by Spielmann in 1948. It is one of the most toxic of the available antiepileptic drugs and should be employed with utmost care. The drug is of unique importance among antiepileptics because it is not only superior to other agents in the control of psychomotor seizures but is also of value in certain cases of grand mal and petit mal (Gibbs). The major side effects are psychic changes, gastro-intestinal symptoms, rash, drowsiness and blood dyscrasias (Tyler and King).

Diamox—Freedom from epileptic seizures has been observed following the administration of diamox (acetazolamide) in a significant number of cases of petit mal and grand mal. It has been postulated that carbonic anhydrase has a role in carbohydrate metabolism of the central nervous system and may conceivably play a part in increasing the speed of the propagation of nerve impulses. It is not as yet clear in what way inhibition of carbonic anhydrase in the brain prevents convulsions. It is possible that inhibition of carbonic anhydrase leads to accumulation of carbon dioxide at the nerve cell membrane and the resulting decrease in the velocity of conduction of impulses may be related to the lowered susceptibility to convulsions.

The best results with diamox to date have been seen in petit mal in children. Good results however, have been observed in some patients, both children and adults, in other types of seizures such as grand mal, mixed seizure patterns and myoclonic jerk patterns.



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Phenaglycodol (Ultran) has been reported to be useful as an effective anticonvulsant agent in epilepsy associated with focal damage (Gruber and Mosier).

2-methyl, 3-orthololyl, 4-quiniazolone has been found to be a most potent anticonvulsant. It is superior to sodium phenobarbital against metrazol-induced seizures and has 80 per cent of the potency of Dilantin sodium against maximal electro-shock (Gujral and Saren). Its clinical value has yet to be assessed.

*Other Factors in the Management of an Epileptic Patient:* Geniuses have emerged from the ranks of epileptics and it is difficult therefore to stipulate rigidly permissible and forbidden mental activity. Patients suffer far more from the very fear of a seizure, solicitude of relations, savouring of pity and the curious attitude of others. The epileptic fears mental deterioration and believes in his own ineptitude in society. The physician has to disabuse the patient's mind on such matters and instil faith and confidence in himself. The patient should be encouraged to read, study, work and pursue safe occupations which are normal for his age. Driving, swimming, operating unguarded machinery, climbing, working on ladders or scaffolding, and working near fire are some of the prohibited activities which may endanger an epileptic's life.

The diet should be simple, regular and abundant in fresh fruits and vegetables. Life need not be made unendurable by imposing a dehydration regimen on the epileptic. Regular bowel habits should be required to be formed. Alcohol does not do any good and certainly not to the epileptic.

Children should be encouraged to attend school. At home a proper parent-child relationship should obtain. Oversolicitude, dependency and hostility are all adverse for the epileptic child. In women, menstrual periods tend to lower the convulsive threshold and a restriction on fluid intake on these occasions might do good. Psychotherapy is necessary for reassuring the patient that his seizures can be efficiently controlled with drug therapy and that there need be no fear of mental deterioration.

In symptomatic epilepsy there is no fear of transmission of tendency to convulsions. In genetic or idiopathic epilepsy the chances of a child of an epileptic parent being affected are reckoned to be one in forty. If epileptic history is traceable in the families of both the parents the chances of the offspring suffering from the malady are certainly greater.

**Summary.**—A brief review of the treatment of epilepsy attempted here will indicate that as far as the available drugs are concerned, none of them confirms to the strict criteria that may be set down for an ideal antiepileptic drug. Most of them are urea derivatives and act as palliatives. Though none of the drugs can cure the disease permanently yet their use has been of immense help to the epileptic in order to keep him free from attacks, and as long as possible. In addition to drug therapy, psychiatric and hygienic measures would be of immense benefit to persons suffering from one or the other forms of epilepsy.

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## EUSTACHIAN TUBE AND ITS DISORDERS

J. V. DeSa

Hypertrophic nasopharyngeal lymphoid tissue is often the cause of some middle ear diseases. The disappointing results of antibiotic therapy and the handicap of diminished hearing raise this problem to vital importance.

The hypertrophy has been recently attributed to viral infection, however, an allergic factor cannot be ignored.

The treatment could be either surgical removal of adenoids or irradiation. Most authors favour surgery to irradiation. Stirk Adams in a study of over 1200 cases of tubo-tympanic deafness following nasopharyngeal lymphoid hypertrophy, came to the conclusion that as many as 90 per cent of cases show improvement in hearing with an operation for tonsil and adenoid resection. If no improvement is seen in spite of the operation, he advises radiation therapy. The incidence of tubo-tympanic deafness in children submitted for the T.A.R. operation is about 12 per cent. The teaching so far has been to postpone the operation till the age of 5-6 years, but recent experience shows that the operation is best done before the age of three.

Support is also accumulating in favour of radiation therapy. The arguments being—the greater accuracy gained in dosage, simplicity of technique, coverage of large area and comparative safety of the procedure. Hardy and Bordley, from a study of 512 cases, were convinced that nasopharyngeal tissue reduces markedly under irradiation therapy and distinct improvement in hearing is gained.

**Techniques of Irradiation.**—Various techniques have been described. Hardy and Bordley used 50 mg radium sulphate applicator for 12 minutes on each side with an interval of 2 weeks or more between 2 successive treatments.

Stirk Adams advises radiation therapy only after the results of T.A.R. operation are ascertained. He prefers radium if the oedema is restricted to the region of the Eustachian orifice and X-rays when the roof of the nasopharynx is involved. The use of platinum filter is recommended instead of Monel metal screen, now popular in America. With platinum screen there is pure  $\gamma$  radiation and the dosage is 500 r from 1 cm distance in 30 minutes, whereas with Monel metal there is 75 per cent  $\beta$  and 25 per cent  $\gamma$  radiation.

**Effects and Hazards of Radiation:** Minute doses of radiation, hitherto regarded as ineffective in this condition, have been found to produce material changes in the biology of hyperplastic lymphoid tissue. Theoretical possibility of some degree of genetic deficiency in the tissues cannot be ruled out easily. Since no local damage was noticed by any author with the usual doses, Stirk Adams finds no objection to continue the use of radium for nasopharyngeal lymphoid hyperplasia.

X-rays, when given in the doses of 1000 r or over, involve a wide area of tissue and have caused in some cases local damage. Moreover, they have not been so effective as radium given in small doses. The use of X-rays is thus deprecated.

## Facial Nerve in Ear Disease

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## FACIAL NERVE IN EAR DISEASE

J. V. DeSa

The facial nerve has, of late, attracted the attention of many otologists. Numerous contributions have been made in this subject and the old views regarding the concept of the lesions, prognosis and treatment are undergoing decisive change.

The signs and symptoms depending upon the anatomical site of the lesion have been elaborately discussed, but rarely do they help in clinical practice and are only of academical importance.

Disturbances of the sensory component are accompanied by pain in and around the ear. In their severe form the pain is referred to the face, pharynx or the tongue or may be a severe and deep-seated localized ache. The former is often associated with herpetic lesions of the external ear and paralysis of the face, commonly called as Ramsay Hunt's syndrome.

Geniculate ganglion neuralgia or tic douloureux of the nervous intermedius, as it is often called, is more painful than herpes. The pain is paroxysmal and a trigger zone could be demonstrated on the posterior wall of the external auditory canal. The differential diagnosis lies between herpes zoster oticus, trigeminal neuralgia and glossopharyngeal neuralgia. In the event of failure of medical treatment, intracranial section of nervous intermedius may prove useful.

Disturbances of motor division. Commonest manifestations are paralysis, twitching or spasm of muscles of the face. Facial paralysis is the most important disorder and may be caused by acute or chronic otitis media, labyrinthitis, cholesteatoma, facial nerve tumours, Bell's palsy, herpes zoster oticus, birth injury, lacerations of the face or surgery of the parotid gland.

**Bell's Palsy:** The aetiology is still disputed. The observations made by Jongkees during facial decompression on a patient who had acute facial palsy of one week's duration form an important contribution. Macroscopic and microscopic findings indicated an acute vascular catastrophe followed by degeneration, exudation of fluid and swelling. The histologic picture was almost identical with that described by Weiss as a result of packing. No evidence of inflammation was found. Kettel also supports this view.

R. Wyburn-Mason believes that Bell's palsy in most cases is the result of a neuritis or irritation of the greater auricular nerve as it lies in the region of the parotid gland. Thus all the old theories, such as based on allergy, oedema, ischaemia, silent otitis media and viral infection still claim support and none so far fully established.

**Facial Paralysis due to Otitis Media and Mastoiditis :** Facial paralysis is a frequent complication of otitic infection. No surgical intervention is indicated when it occurs during the course of acute otitis media. But when acute purulent otitis media is complicated by mastoiditis and facial paralysis, a simple mastoidectomy in addition to antibiotic therapy is indicated. If the facial nerve function does not recover within 2 months, facial decompression is advised. Even in chronic suppurative otitis media complicated by seventh nerve palsy, immediate mastoidectomy will be all that is necessary. Facial decompression should be done if there is no recovery within two months and response to Faradic stimulation has waned.

**Post-operative Palsy :** The paralysis may supervene immediately after operation due to direct trauma. The cause may be laceration or section of the nerve. Exposure of the nerve is indicated since it gives opportunity to detect the cause. If only a bone spicule is jammed in the fallopian canal, its removal may be enough. If however there is breach in the continuity, end-to-end anastomosis must be done. If the ends cannot be apposed re-routing or grafting is indicated after 3-6 weeks.

When the paralysis is seen 12-24 hours after the operation, the cause is mostly oedema and nothing more than removal of the mastoid dressing is usually required. If positive, Faradic response can be elicited for 2 weeks and a satisfactory recovery can be anticipated.

**Surgery of the Facial Nerve.**—Lathrop (1953) described the technique of exposure and repair of facial nerve. He utilizes the relation of the facial nerve to the stylomastoid foramen when exposure is desired within the mastoid process. The nerve also can be isolated extracranially or within a mastoidectomy cavity. In the former case, the posterior belly of the digastric

muscle in the digastric groove is a guide, but when this is difficult the stylomastoid foramen is located by probing the anterior portion of the digastric groove and the nerve traced from there.

Exposure at the stylomastoid foramen through a mastoidectomy cavity is more difficult but is advantageous for the management of injury, tumour, hemifacial spasm or Bell's palsy.

Exposure of the nerve in the neck and face is best considered in relation to the parotid gland. The nerve can be traced either crossing the styloid process or posterior to it. Once the trunk of the nerve is isolated, the branches can be traced within the parotid gland and onto the face.

The facial nerve also could be traced by following the posterior facial vein beneath the inferior border of parotid, until it is crossed by the inferior-most branch of the nerve on its lateral surface. The nerve is then traced through the parotid gland by delicate dissection.

The treatment of traumatic facial nerve palsy consists in either end-to-end anastomosis, grafting or re-routing. In re-routing, hypoglossal anastomosis is preferable to accessory.

**Paroxysmal Hemifacial Spasms.**—This is the opposite of paralysis and is supposed to be due to a degenerative lesion at or below the geniculate ganglion. The spasm is clonic and involves the eyelids first. Other muscles are involved later. It is differentiated from facial tic of compulsion neurosis by the facts that the former affects only the muscles supplied by the facial nerve, has no relationship to psychological stress and that the spasms occur during sleep also.

It must also be differentiated from hemifacial spasms secondary to other lesions of the facial nerve, such as Bell's palsy and intracranial aneurysms. The patients with hemifacial spasms are miserable and handicapped. The treatment has been so far worthless. Spontaneous remissions are known. Decompression has been helpful in rare case.

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**FACIAL PARALYSIS IN LEPROSY**—See LEPROSY, FACIAL PARALYSIS IN

**FIBROPLASIA, RETROLENTAL**—See RETROLENTAL FIBROPLASIA

**FIBROSARCOMA OF LUNG**—See LUNG, FIBROSARCOMA OF

**FILARIASIS, CLINICAL ASPECTS OF**

*R. Subramaniam*

Alhadeff's paper deals with filariasis as observed in a selected group of 33 cases. The filaria was identified to be *Wuchereria bancrofti*. The study was undertaken in an attempt to understand the earlier symptomatology of filariasis. Most of the cases were from Mauritian troops stationed in the Suez Canal Zone who were admitted in the British Military Hospital at El Ballah between 1950 to 1952.

The clinical manifestations observed were general debility, lymphadenitis, inflammation of the genitalia, urinary infections, chyluria, lymphangitis, abscess of muscles, synovitis, filarial colic and filarial peritonitis.

General debility was observed from a few weeks to many months, and was associated with symptoms like malaise, insomnia, weakness and numbness of the lower limbs. Nocturnal pains were experienced in the inguinal region, testicles, knees, thighs or axillae. A marked mental depression was also observed.

Adenitis was usually met with in the inguinal, axillary and epitrochlear regions. The glands were firm, tender and matted and only moderately enlarged, the overlying skin was hot and sometimes adherent. In the inguinal region, the lymphadenitis may be sometimes be mistaken for a femoral hernia.

The inflammation of the genitalia was a common condition for which the patients had to be hospitalised. A feeling of scrotal heaviness, abdominal pain referred to the thighs and knees were noticed, in about 50 per cent of the cases. Spermatic cord, epididymis and testicles were

## Filariasis, Eosinophilia in

affected. Long inexplicable fever occurred in one case who ultimately developed an inflamed varico-lymphocele. The epididymis, when involved, was usually very painful, tense and smooth, but never craggy or adherent to prostate. This feature distinguished filarial epididymis from tuberculosis. When the testes were affected they enlarged rapidly and subsided after a period of one to 3 weeks leaving only some thickening of the structures involved but no testicular atrophy. Secondary hydrocoele sometimes developed and the exudate showed a high eosinophilic content and the presence of microfilaria.

The urine was found to contain pus cells in all the 13 cases, and staphylococcal, streptococcal and B.coli could be isolated from it. Urinary infection occurred only when there was visceral involvement and so this can be used as an index of the extent of visceral involvement.

Chyluria was found in 7 cases and it was intermittent. The urine coagulated quickly, and on the top layer floated white fat and below there was a pinkish sediment containing red cells. In the coagulum, microfilaria were seen. These patients often complained of pubic heaviness, backache and pain in the thighs. Anaemia due to haematochyluria was present in one patient.

Cystoscopy performed in 4 cases revealed various degrees of catarrhal cystitis.

The diagnosis in many of the cases was obvious from the clinical condition, and during night from examination of blood collected for microfilariae. The method employed was to put one large drop of blood in a concave slide, haemolyse it with two drops of water and examine under low power of the microscope. The eosinophil content of the blood varied from 5 to 15 per cent where the microfilaria was not demonstrated. The diagnosis was arrived at with *Dirofilaria immitis* antigen. This antigen is not an absolute test as it was found to give a negative reaction with certain clinical conditions.

*Treatment* : Sulphamezathine was found very useful in the control of inflammatory lesions. Filarial hydrocoeles were excised through a scrotal incision. Treatment of urinary sepsis remarkably ameliorated the associated chyluria. The author is not in favour of restricted fluid or fat. The patient is already suffering from a mechanical loss of fat and no useful purpose is served by reducing fat intake. Diethylcarbamazine (Banocide) in oral doses of 100 mg thrice daily for 21 days was found to have remarkable influence on the number of circulating microfilariae. The action of this drug on the parental worms is uncertain and recurrences are due to their survival.

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## FILARIASIS, EOSINOPHILIA IN

R. Subramaniam

Helminthic infestation has been known to be responsible for a rise of circulating eosinophils to a variable degree. The association of eosinophilia and filariasis is frequent but the extent of the former and its relationship to the latter remain to be settled. The authors have studied a series of 1340 patients of different age-groups, the ages ranging from 1½ to 72 years. The patients showed various clinical manifestations of filariasis viz., lymphangitis of the legs, arms, genitals, breasts with or without elephantoid changes, epididymo-orchitis, funiculitis, lymphadenitis, lymphadeno-varix, hydrocoele and chylocoele, chyluria, urticaria, etc. The duration of illness varied from 15 days to 30 years. *Microfilaria malayi* was found in three, while in the rest *Microfilaria bancrofti* was found. The percentage of eosinophils as registered by the differential count of blood from the above patients varied from 0.5 to 60 as follows :

Eosinophils	Cases
0-5 %	39.4%
6-15%	45.5%
16-25%	11.2%
26-40%	3.3%
40-60%	0.4%

The percentage of cases with the results obtained did not show any significant relationship of eosinophilia to filariasis.

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## GALACTOSAEMIA, CONGENITAL

J. B. Mehta

This is an inborn error of metabolism in which galactose is not metabolised by the liver and galactosaemia and galactosuria occur. Normally galactose is converted by the liver to glucose by an enzyme phospho-galacto isomerase or transferase which may be deficient in this disease. The excess of galactose in the blood seems to have a toxic effect and produces liver damage, cataract formation and mental retardation. It may be remembered that galactose is a constituent of cerebroside paradoxically. Aminoaciduria may also be due to toxic effect on the renal tubules as it disappears on treatment<sup>1,2</sup>.

The clinical picture is that of an infant who soon after birth refuses its feeds and fails to grow. Jaundice, hepatomegaly, splenomegaly, lamellar cataract and mental deficiency are present. Aminoaciduria is associated. Osteoporosis of the bones may be present. It is often familial. Examination of the urine in all cases of jaundice, hepatomegaly and marasmus is stressed, more so as early treatment is effective. Galactosuria has to be distinguished from glycosuria by chemical test, osazone crystallisation and easier still by paper chromatography.

Lactose-free milk or diet is prescribed. This is difficult as milk has to be excluded from the infant's diet and a gruel mixture of cereals or soya beans, arachis oil or margarine, glucose and water has to be prepared. Casilan (milk protein) may be substituted but it contains about one per cent lactose. Low lactose containing milk powder (Trufood) is also available.

The danger of doing a galactose tolerance test in these children is stressed and Manchanda's case seems to have ended fatally after such a test was performed. His is the first reported case in India<sup>2</sup>.

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## GASTRITIS

S. Sachdev

*Gastritis, Hypertrophic*: Two cases of hypertrophic gastritis are described<sup>1</sup> by the author who has also reviewed 50 proved cases from literature. The symptomatology, diagnosis, perplexing pathological features and the treatment are described. Follow-up period has been short. The cardinal symptomatology includes pain, loss of weight, vomiting and haemorrhage. On the average the symptoms are present for two years before the patients require surgical intervention. Pain is usually present in the epigastrium and occurs an hour or two after meals and is occasionally relieved by food or alkali. During the course of this disease the average weight loss is about 15 lb. Hypertrophic gastritis has a strong tendency to become chronic and heal poorly. Complications are rare except for the tendency to haemorrhage which occurs in quite a few patients suffering from this. Differential diagnosis presents considerable problems. The condition has to be differentiated from a malignant lesion and many other organic and functional diseases. Histological examination is necessary to decide the diagnosis. A pathological classification is submitted. It includes hyperplasia of the surface epithelium, interstitium of mucosa and sub-mucosa. Overlapping of various types and mixed pictures occur. The problem of sequential relationship between hypertrophic gastritis and gastric carcinoma has been mentioned. Surgery is indicated in this condition in which the criteria for selection are the same as in gastric ulcer, e.g. the possibility of malignancy, persistent pain, repeated haemorrhages and obstruction.

The second investigation (Edwards and Edwards)<sup>2</sup> was undertaken to determine the effect of very hot drinks on gastric mucosa in subjects attending the Central Middlesex Hospital, London. These patients were 155 in number and gastric biopsy had been recently performed on them because of dyspepsia. Histologically, the specimens were classified as normal in 78 cases, superficial gastritis in 9, atrophic gastritis in 36 and miscellaneous in 32. A cup of boiling tea flavoured to taste, was given to each subject who was asked to sip it frequently when it had cooled to the temperature at which it was usually drunk. A record of this temperature was kept and the observer was not aware of the biopsy report in most cases.

The temperature of the tea drunk by patients and the mucosal abnormalities showed a relationship which could not be explained by the age and sex of the subjects. In patients under 50

## Gastro-intestinal Tract, Tuberculosis of

years, only 2 out of 13 who drank tea when it was below 122.5°F (50.27° C) had an abnormal mucosa, while 14 out of 18 who drank tea when it was 137.5° F (58.6° C) had an abnormal gastric mucosa.

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## GASTRO-INTESTINAL TRACT. TUBERCULOSIS OF

K. S. Aiyer

A review of this subject is beset with many hurdles, one of which is the lack of available statistical data. Though a large volume of literature was consulted and much general benefit derived the paucity of specific information was striking.

Tuberculous lesions in the oesophagus and stomach are very rare. Apart from local manifestations of miliary disease, isolated ulceration of the oesophagus or the stomach must be considered an oddity. All such lesions are definitely secondary like in the rest of the gastro-intestinal tract, and in the vast majority of cases are but milestones of complications on the downward terminal path. The swallowing of tuberculous sputum or extensions from neighbouring lymphatics are adduced as aetiological factors. It will be interesting to note whether in the terminal phase when there is every likelihood of achlorhydria, the organisms really take hold and produce multiple or single lesions. Autopsy findings from tuberculosis sanatoria will be interesting and serial sections by pathologists may throw further light.

In the small intestine, tuberculous lesions are commonest in the ileum, less so in the jejunum and rare in the duodenum. In our experience we have on record two definite instances of tuberculous strictures occurring in the jejunum causing obstruction (Figures 1 and 2) but even so this was not an isolated lesion but was associated with encircling lesions and strictures in the ileum. Though ulceration can take place a circumferential lesion with fibrosis and subsequent stricture is the commonest finding. It is usually said that perforation is unknown, but the reviewer must go on record as having operated on a case with perforation proximal to a stricture in the ileum causing intestinal obstruction.

Enlargement of the mesenteric glands is another common finding in the abdomen. Extensive involvement of the greater omentum is an associated condition and together they constitute a typical symptom-complex. Removal of a mesenteric gland for biopsy is not free from danger, and as an isolated procedure is rarely resorted to. The necessity for biopsy to establish diagnosis is not essential except when mesenteric lymphadenitis is the only finding on laparotomy. Caseation and the formation of adhesions and bands follow and constitute another danger. The three important causes of surgery in tuberculosis centre around stricture, bands and adhesions. Ulceration and consequent intractable diarrhoea demand the services of the physician, while intestinal obstruction calls for active surgical intervention. In our experience 15 per cent of all cases of intestinal obstruction are due to bands and adhesions caused by tuberculosis, while strictures of tuberculous origin account for less than 5 per cent.

From time immemorial, the caecum has been designated as one of the common sites of tuberculous infection (Figure 3). It has been customary to talk of an ulcerative type and hyperplastic type. The latter is open to question and it is now generally held that this is a manifestation of Crohn's disease. The reviewer has never met a pure hyperplastic tuberculous lesion in the caecum. In a great many instances of caecal lesions the primary lesion is either quiescent or of such antiquity as to have escaped notice.

Diagnosis of ileocaecal tuberculosis is not difficult, but is usually delayed, as patients do not consult the surgeon until definite episodes of pain and chronic obstruction occur. A slow decline in general health and an insidious alteration in the bowel habit do not alarm patients unduly. Obstructive symptoms occur only very late as the intestinal contents are still fluid. Acute obstruction is particularly unknown, which is sharply at variance with the history of neoplasm. The intense anaemia which is a concomitant of malignancy in this region, is absent except in the late stages of tuberculosis. Roentgenological examination usually enables an accurate diagnosis when read along with clinical signs and findings including E.S.R. To be academic Mantoux's test may be mentioned.

*PLATE III*

TUBERCULOSIS OF GASTRO-INTESTINAL TRACT

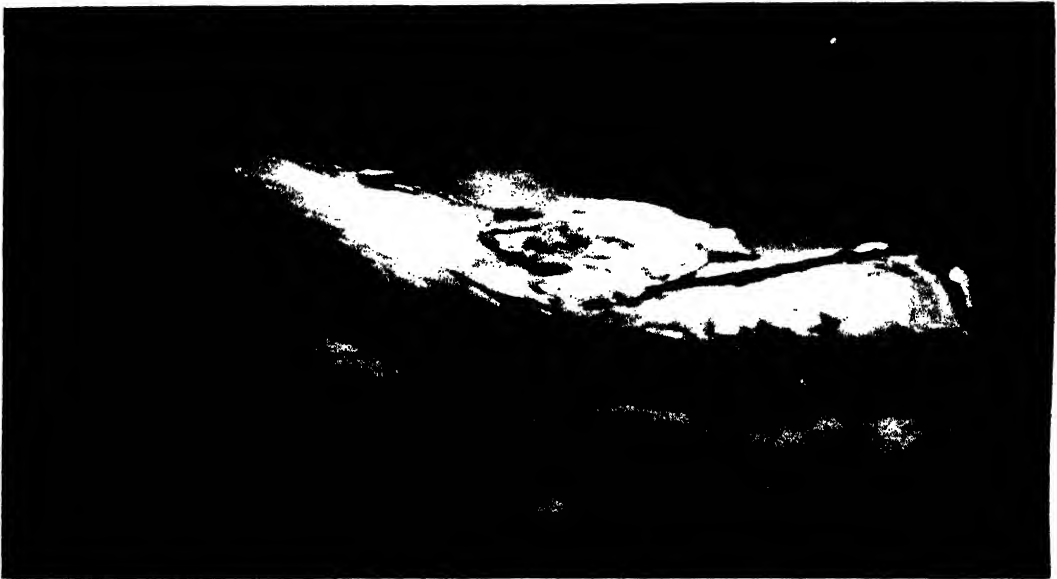


FIG. 1

*Tuberculous stricture of the jejunum. The marker points to the stricture*

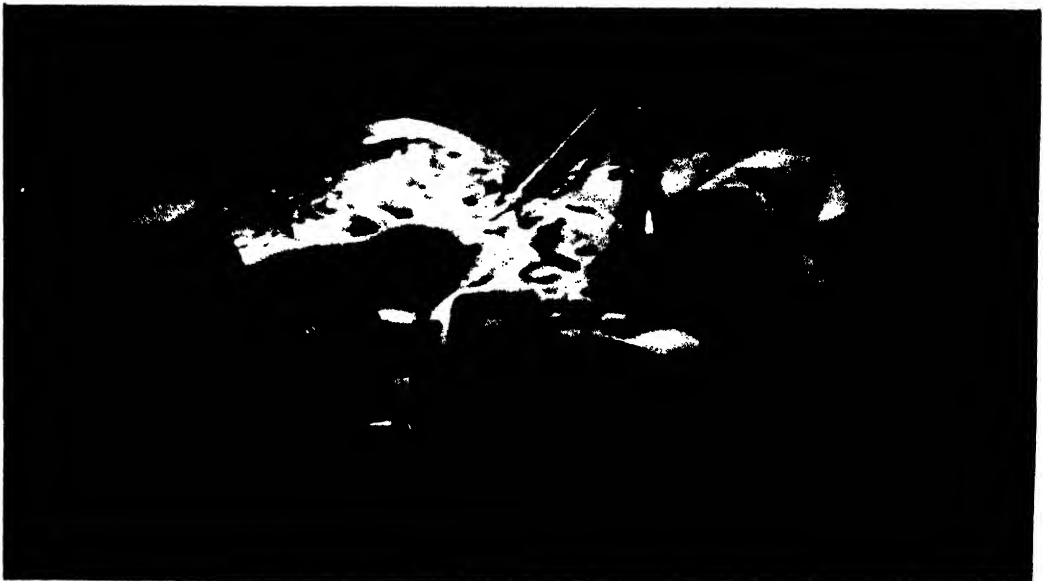


FIG. 2

*Section of the specimen showing the stricture in the jejunum.*



*PLATE IV*

TUBERCULOSIS OF GASTRO-INTESTINAL TRACT



FIG. 3

*Ileocaecal tuberculosis. The marker points to the base of the appendix.*

In regard to treatment the general medical care and chemotherapy need only be lightly touched upon. The value of streptomycin is difficult to assess, in view of the fact that gastro-intestinal tuberculosis is quite slow in its progress, and is also subject to remissions. As a general rule the average total dose appears to be 100 g suitably spaced. The intake of P.A.S. at the rate of 12 g daily is advisable. The more spread out streptomycin therapy is, the better seem to be the results. Adjuvants like I.N.H. are helpful.

The ideal surgical treatment of tuberculous lesions should be radical removal of the affected portion of the gut with restoration of the continuity. It was very common in the thirties and forties for bypassing operations to be performed frequently. In caecal tuberculosis exclusion of the caecum was also carried out. The patients seemed to do well. We have no statistical data as to the end results. Such a procedure will now be considered good. A short-circuiting ileostomy or ileo-transverse-colostomy can only be deemed to be a palliative measure to be undertaken when the general condition of the patient will not warrant a more radical operation. We have ourselves excised three and four strictures in the small gut at one sitting with a restoration of continuity without any adverse effect on convalescence. In an ileocaecal tuberculosis preference should be given to removal of the last one foot or 18 inches of the ileum, the caecum, the ascending colon and the right half of the transverse colon with ileocolostomy. There is a tendency among surgeons to argue at length about the relative merits and demerits of end-to-end, end-to-side and side-to-side anastomosis. Such arguments appear to the reviewer as needless and pointless. Depending on the local conditions any one of these can be performed with equally good results. Careful pre-operative preparation aimed at restoration of electrolyte balance and haemoglobin levels by transfusions are considered the most essential prerequisite to a successful result. The reviewer never undertakes operations without one or two transfusions as a routine procedure. With such preoperative care and the selection of suitable cases mortality can be expected to be in the region of 7 per cent. In many clinics and hospitals it is probably much less. In our last series of 15 cases there has been no death.

Tuberculosis of the large gut apart from the caecum is rare. The reviewer has notes of only one case of tuberculous stricture in the transverse colon which simulated neoplasm. Tuberculous ulceration of the rectum does occur. They present the ragged undercut edges and may even be quite extensive. Bacilli are present in the discharge and healing rarely if ever occurs. Tubercular spread along the lymphatics to the para-rectal region is common in progressive lesion and should occasion no surprise. They finally result in intractable multiple fistulae. Their occurrence is a sign of grave import. Their treatment will be dealt with in the section on fistula-in-ano.

I would like to conclude on a cautiously optimistic note. Chemotherapy and surgical treatment must be considered as merely steps, no doubt concerted, in encircling the foe. Treatment must necessarily be prolonged if it is to be successful. Even after such treatment it will be wisdom on the part of the patient to enter a hospital or a clinic at intervals for a check-up. This way lies safety.

**Regional Ileitis (Crohn's Disease).**—It is hoped that the reviewer will not be accused of stirring up a hornet's nest when it is mentioned that this condition is not quite so rare as it was once believed to be. It must also be conceded that while the ileum remains the favourite site, the condition occurs quite frequently in the jejunum and the caecum. Much interest of late has been focussed on this subject by the occurrence of this condition in a distinguished President of the U.S.A.

It is well to remind ourselves of the pathology of this condition. The causation is unknown. Theories have been advanced that this is due to a form of streptococcus, that it is due to a form of tubercle bacillus, that it is due to a type of dysenteric organism or that it is due to a virus infection. It is doubtful if any one of these is really tenable. However, it is true that there is a striking resemblance of the lesion to those of a non-specific granuloma and that typical 'tubercles' are absent on microscopic examination. There is absolutely no proof in support of any specific agent, and so the customary label of virus infection is attached to it. That the lesions have a superficial resemblance to those of lymphogranuloma inguinale cannot be denied. But Frei's test is negative in all cases. Again like ulcerative colitis there is a tendency to episodes of acute exacerbations and remissions. Only certain areas of the bowel seem to be affected, the intervening portions remaining absolutely normal in all respects.

## Genito-urinary Tract, Radiological Aspects of

Different stages of the disease are mentioned, but it is unnecessary to dwell on them all. There is no doubt that the acute phase resembles acute appendicitis and it is probable that a proportion of appendicectomies done are for Crohn's disease. It will be interesting, if in all cases of appendicectomies, where the appendix exhibits no obvious pathological changes, the small and large intestines are closely examined. Many latent cases of Crohn's disease may be expected to come to light. There is a palpable mass in the right iliac fossa when the ileocaecal region is involved. There is usually a narrowing of the lumen of the affected segment which may be so extreme as to produce the typical X-ray findings of a 'string appearance'. While melaena is a feature of the acute phase, recurring attacks of diarrhoea and passage of mucus are characteristic of the subacute and chronic phases. There are episodes of abdominal pain and vomiting. Loss of weight is significant. Obstruction, perforation and fistulae may result. General peritonitis is rare but localised abscesses may form.

Spontaneous recovery is rare. But intervals of freedom are common. In the usual phase with which cases come to the operation table, the affected segment of the bowel looks and feels like a hose-pipe. Treatment should aim at being as radical as possible, the affected areas being removed and the continuity of the bowel being restored. When there is any reason to doubt the general condition of the patient a 'bypass' operation is undertaken with the possibility of a second stage resection. It is curious however, that a two stage operation does not appreciably decrease the morbidity. It is to be remembered that the pathology denotes a progressive lesion and the patient's condition tends to deteriorate in spite of the first stage bypass. A single stage radical resection is attended by good results. The overall mortality is usually about 20 per cent.

The distressing feature of this disease is its proneness to recurrence. It may recur after surgical resection at any time upto six years or even longer. But in the vast majority, symptoms of recurrence become apparent within two years. The same symptoms as in the original disease appear, thus heralding a flare-up. Approximately one-third of all the cases recur, another segment of the bowel being affected, necessitating further surgical procedures. A further recurrence seems to take place in half the number of such patients. Ian Aird reports an extreme case where the same patient had four operations, each time a different portion of the bowel being resected.

Pre- and post-operative transfusions help convalescence. A valuable tip is to cut down post-operative fat intake. This usually brings about abatement of the diarrhoea and improvement in the patient's general condition. All patients must be made to realise that they face a long convalescence similar to patients with pulmonary tuberculosis. Bed rest and sanatorium treatment, ample nutrition and supplemental vitamins have a useful place. Antibiotics do not seem to act specifically. ACTH and cortisone have been disappointing as a cure but may have some value as supportive measures.

The question of nutritional defects following resection of large portions of the small intestine has always exercised the minds of surgeons in their approach to removal of affected segments. Anaemia is another result that may have to be energetically treated. Hypocalcaemia has also been reported severe enough to produce tetany. Fortunately, this can be controlled by calcium and large doses of vitamin D. All in all, there is little doubt that surgery does offer relief to obstructions due to granulomatous changes and the occurrence of fistulae which cannot be closed by any other *modus operandi*. Again, there is no doubt that resection is the ideal treatment, in contrast to the palliative short-circuiting. Finally, it must be conceded that radical surgery is but half the battle and a return to normal can be expected only after careful and prolonged medical regimen.

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## GENITO-URINARY TRACT, RADIOLOGICAL ASPECTS OF

M. G. Varadarajan

**Value of plain film in renal lesions.**—Attention to renal contours in plain films will be one way of advancing diagnosis of renal masses in symptomless survey cases according to Alice Ettinger

and Milton Elkin (1954)<sup>6</sup>. Roentgen visualisation on plain film was found to be superior to physical examination by palpation when all cases were considered.

The type of calcification does not permit a diagnosis of exact nature of the renal mass. A case of a calcified tumour of the right kidney which proved on biopsy to be adenocarcinoma of the right kidney has been reported by Varadarajan (1956)<sup>18</sup>.

Srivastava (1956)<sup>15</sup>, with reference to 'prostatic calculi' has stated that much is known about renal and bladder calculi but little importance is attached to prostatic calculi which are not as rare as is generally thought. If a routine investigation is carried out and an X-ray of the region of the prostate is taken, a large proportion of cases of prostatic calculi associated with some abnormal pathology of the gland will be recognised.

Two types of prostatic calculi are described: (1) true or endogenous; (2) false or exogenous. The former occurring in the substance of the gland and the latter in the prostatic urethra. The true (endogenous) is more common. It is rare before the age of 30 years. The stones are composed of organic matter consisting of protein, cholesterol and citrate and inorganic matter consisting mostly of tertiary calcium phosphate, with small quantities of calcium oxalate, carbonate or uric acid. The nucleus of true prostatic stone is composed of organic material of an albuminoid nature and not pure protein. The size of the stones varies from that of a grape seed to that of millet and the colour varies from light grey to dark brown. The author advises a routine X-ray of all cases with prostatism to diagnose cases of prostatic calculi and get an idea of its frequency in India.

Reports on "Hypaque", a new urographic medium—800 cases have been reported by Eugene Speicher (1956)<sup>14</sup>. This medium yields a high percentage of diagnostically satisfactory urograms while causing a minimal amount of side reactions. Harrow (1956)<sup>7</sup> has stated that a concentration of 50 per cent has proved to be excellent with minimal side reactions. The most important factor in obtaining excellent urograms is the proper use of adequate compression for two minutes in the hypogastrum.

*Hysterosalpingography—Media for the Procedure*: The continued interest shown in the use of new media for this radiographic examination, suggests that no entirely satisfactory substance has yet been evolved although it is over 45 years since Rhindfleish (1910)<sup>12</sup> first visualised the outline of the uterine cavity with bismuth paste. Iodised oil was applied to gynaecological problems by Houser (1925, 1926)<sup>8</sup> and remained the sole agent employed for many years. The disadvantages of this include the danger of embolism, extensive foreign body reactions within the tubes and in the peritoneal cavity. Davies, Fisher and Rocker (1957)<sup>5</sup> have tried "endografin" which is an aqueous solution of the methyl glucamine of N: N-adipic-(amino-2 : 4 : 6 : triiodobenzoic acid) in 75 cases, with their special technique. The complications encountered in this procedure are pain and peritonitis : pain may occur in the first 24 hours or later. The authors felt that the occurrence of pain can be prevented by using the minimum amount of medium required for good radiographic visualisation. While the production of pain is certainly a great disadvantage, they feel that in view of other advantages, e.g. adequate contrast, easy injection, no tendency for the substance to crystallise out of solution, complete absorption in two hours after the injection, no warming of medium before injection and giving rise to no undue tubal spasm, it deserves an extended trial. Others favour Viskiosol and Salpinx.

The effect of a full urinary bladder in hysterosalpingography is recorded by Blight and Williams (1956)<sup>2</sup>. The position of the fallopian tubes can be influenced by a full urinary bladder and a distended bladder may cause a picture resembling hydrosalpinx. Much valuable information regarding the mobility of the tubes may be obtained by noting the varying degrees of bladder distension. If a significant degree of bladder filling is shown on any film, the bladder should be emptied, preferably by catheterisation before the examination is concluded.

*Delayed Spill in Hysterosalpingography*: Coopersmith (1955)<sup>3</sup> in at least three cases in which (lipiodol was used) there was no spill on the 24 hour film, a subsequent X-ray study showed the oil in the peritoneal cavity. When mild obstruction exists the oil may probably exert a therapeutic effect. Therefore if at the end of 24 hours, oil is present in the tube but has not "broken through" the fimbriated end, further X-ray follow-up is indicated. It is suggested that if obstruction is found at the fimbriated end of the tube, repeated oil patency test should be tried before surgery is contemplated.

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Hystero-graphy, as one of the most valuable methods for detection of uterine fibroids and especially of the submucous variety has been discussed by Rozin (1956)<sup>10</sup>. He is of the opinion that this method enables a differential diagnosis to be made between interstitial and submucous fibroids and gives information on the localisation and size of the tumour, the distortion of the uterine cavity and other abnormalities. It is thus helpful in enabling us to decide between surgical and non-surgical treatment and when operation is decided on, it serves as a guide in the choice of radical or conservative intervention. This is important specially in cases of sterility or repeated abortions and here the information on the patency of the tubes is of considerable value since the decision for conservative surgery in sterile women is dependent upon it. The value of this procedure is all the more useful when it is realised that the diagnosis of submucous fibroids or myoma is often difficult clinically. The author describes the technique he has followed, the characteristic features of submucous fibroids in the uterograms, and the differential diagnosis of submucous fibroids from other pathological causes of intra-uterine filling defects.

Barnett (1956)<sup>1</sup> while discussing the clinical value of hysterosalpingography, states that X-ray appearance in tuberculous endometritis is not pathognomonic. In the assessment of tubal patency, this is superior to the carbon dioxide insufflation test. However from the practical aspects, these tests are complementary and therefore, should be utilised when the problem of tubal patency is being considered. The author states that the proper selection of iodised oil or water-soluble media in accordance with the clinical indications permits the maximum information to be obtained. Lipiodol is the medium of choice when the purpose of the examination is the exclusion of an intrinsic uterine anomaly. It is felt that there is little likelihood of a significant peritoneal reaction with the small amounts of lipiodol used for these patients. In cases where tubal pathology or a pelvic mass is suspected, a water-soluble medium, e. g. Viskiosol '6' is the most suitable.

The author considers that pelvigraphy can be used as a routine procedure in cases of suspected pelvic mass without necessitating a prolonged examination. This procedure may not add to the clinical diagnosis in many cases but in others will indicate the site of origin of the mass, a fact which may be doubtful clinically or can aid in excluding the presence of a pelvic mass. In the demonstration of hydrosalpinx, hysterosalpingography has proved to be of the utmost value. A water-soluble medium is therefore the one of choice.

*The Clinical use of Radiology in Placenta Praevia (a review of 433 cases of antepartum haemorrhage examined radiologically, 1951-1954)*: The increased utilisation of radiology in the diagnosis of placenta praevia by soft tissue radiography is recorded by Davidson and Lindsay (1956)<sup>1</sup>. It can be diagnosed with accuracy at an estimated duration of pregnancy of 32 weeks or over.

The principle underlying the modern radiological technique is simple—the placenta occupies space: when there is no space available, there is therefore no placenta; where there is space available, it is possibly occupied by the placenta. In investigating a patient in whom placenta praevia is suspected, an attempt is first made to show that there is no space between the presenting part and the brim of the pelvis and thereby placenta praevia is excluded. If there is space between the presenting part and the brim of the pelvis, other explanations such as a full bladder or rectum or soft tissue tumours must be considered and excluded.

The technique adopted relies entirely on straight radiography with the foetus acting as if it were a contrast medium. X-rays are taken with the patient in such a position that the foetus is above the suspected soft tissue shadow. This soft tissue technique has been described in various publications (Whitehead, 1953<sup>17</sup>; Reid, 1949 and 1953<sup>11</sup>). Difficulties arise when there is a relative excess of liquor amnii masking the placenta as in early pregnancy and in hydramnios. Extrinsic soft tissue masses are confusing and it is therefore important that the bladder and rectum be emptied prior to radiological examination. Other soft tissue masses such as uterine fibroids or ovarian cysts simulate the placenta and their presence can only be suspected radiologically by their shape and position. When these complications are not present, the information obtained from the radiological examination is definite and reliable.

The author concludes that nearly 100 per cent accuracy can be achieved in excluding placenta praevia; a high degree of accuracy is possible diagnosing uncomplicated types II, III and IV

placenta; in type I placenta praevia or in the presence of malpresentation, hydramnios, a small or deformed foetus, and fibroid, the radiological findings may be uncertain. The author emphasises the value of looking for the placental site on all routine radiological examinations in obstetrics especially when the radiological technique is possible in any general hospital X-ray department.

*Placentography in the Management of Placenta Praevia:* Watson and his associates (1957)<sup>16</sup> have presented 80 cases in which placentography was performed for clinical reasons with an accuracy rate of placental location of 94 per cent. No wedge shaped filter was used.

Investigation on localisation of placenta by soft tissue technique, has been started since the beginning of the year (1957) in the Government Hospital for women and children, Egmore, by Varadarajan, and the results are encouraging.

**Pelvimetry.**—The Assessment of the type and size of Indian female pelvis<sup>17</sup>: In this investigation only nulliparous and primigravidae were taken up for assessment by X-ray pelvimetry. Using Thoms's classification, the distribution has been found as follows—dolichopellic—25.7 per cent; meastopellic—49.3 per cent; brachypellic—23 per cent and platypellic—2 per cent. The maximum and minimum anteroposterior diameters (in cm) of the inlet were found to be 12.88 and 9.17 in dolichopellic, 12.88 and 9.55 in meastopellic, 11.35 and 9.15 in brachypellic and 10.0 and 9.6 in platypellic types.

Technique for Routine Pelvimetry with the use of single X-ray film is discussed by Thoms and Billings (1956) who believe that every primigravida should have the benefits of a survey of the bony pelvis. Clinical examination alone cannot be relied on in all instances to disclose pelves that require X-ray assessment. However, solely for screening purposes as a routine procedure, palpatory measures plus a single X-ray film can furnish enough information. Use of the lateral film is omitted, it being reserved for instances in which further information is desired concerning pelvic morphology, more definite information is desired concerning antero-posterior diameters at all levels and it is desired to study cephalopelvic relationships. The inlet and midplane assessments are made on a single X-ray film obtained according to the Thoms-Wilson technic. Two corrected centimeter scales appear on the film. The uppermost scale represents the correction for the plane of the inlet and the lower scale represents that of a plane 7 cm below this level, at that of the ischial spines. Experience has shown that correction at this seven cm level is accurate enough for all obstetric purposes provided the target-film distance is maintained at 36 inches. For routine pelvimetric assessment such a screening plan makes possible the separation of pelves into two groups: (1) pelves that have shown to have adequate capacity for the passage of a normal full term foetus and (2) pelves in which further X-ray study is desired to complete the pelvic survey.

*X-ray Pelvimetry:* Prediction of the outcome labour using a new method<sup>18</sup>: The roentgen-pelvimetry as a scientific aid can be of practical importance to an average obstetrician and general practitioners only if it works out the relationships between the determined size and shape of the pelvis and the actual outcome of labour in simple mathematical forms. The present study is an attempt in this direction and the average size, a body weighing 5½ lbs.

The parallax method, as used in the present study, aims at obviating this difficulty by taking two plates under standard conditions with shifting of the X-ray tube by ten centimeters between the two exposures. Two plates together are interpreted through mathematical calculations using special formulae and tables. Two measurements are taken at each of the three principal planes or levels of the pelvis viz. inlet, midcavity and outlet. At the inlet, the two measurements are the A-P and maximum transverse diameters. At the midcavity and outlet, the diameters are transverse and posterior sagittal (P. S.).

It has been found that the arithmetical sum of the A-P and transverse diameter at any given level is a more reliable index of pelvic capacity than the individual diameters themselves. This arithmetical sum, for convenience, is called the index for that plane. An index is calculated for each of the three levels. Thus, for the inlet, the index is equal to A-P and transverse diameters and for the midcavity and outlet, index is equal to P. S diameter plus transverse. The normal measurements and indices for Indian women as worked out by Desouza at various levels are as follows :—Inlet : A-P 11 cm. Trans. 13 cm. Index-24 ; For cavity : Trans. 9 cm ; P. S. 6 cm. Index-15 ; Outlet : Trans. 10 cm ; P. S. 6 cm. I-16. In this study

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all the cases were divided into four main groups using the following criteria as the basis for grouping:

	Inlet index	Midcavity index	Outlet index	Prognosis
Class A .. .. .	Above 22	Above 15	Above 16	Good. Vaginal delivery.
Class B .. .. .	21-22	14-15	15-16	Fair. Vaginal delivery is usual.
Class C .. .. .	20-21	13-14	14-15	Guarded. Operative interference usual.
Class D .. .. .	Below 20	Below 13	Below 14	Vaginal delivery is out of question.

45 cases were studied using the above method of analysis and prediction and conclusions are— (1) operative delivery is seldom required when the inlet index is above 22, (2) Live, vaginal delivery even operative, seldom occurs when the inlet index is below 20.

The proper way to evaluate any method will be to study the individual predictions rather than the statistics. Like all tools, pelvimetry can be precise or inexact, beneficial or dangerous according to the knowledge, skill and experience of the user.

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## GERIATRICS

D. V. Doshi

The problems of aging have not been studied much in India as they have not assumed the huge proportion attained in advanced countries. The average life span of an Indian is also much lower. The Royal Commission on Population in Great Britain published its report in 1949 and it gave some revealing facts. The population aged over 65 years in Great Britain was one million in 1851, 2.1 million in 1911, 4.2 million in 1939, and 5 million in 1947. With the prevailing mortality rates, it is assumed that by 1977, this aged population would rise to 7.3

million. With the advent of antibiotics and improvement in mortality figures, the pattern of general practice in medicine has been changing. One would have to deal with ravages of age oftener. The liability of elderly persons to get ill is about three times the adults. The normals, the pathology, the clinical manifestations of the aged are also at times varying from adults—and hence a special study is required. Social problems of the aged are also equally difficult to tackle, and even the governments have taken active steps in the Western countries to solve these problems.

There are certain peculiarities attached to these problems of aging :

- (a) Multiple pathology: Changes in the body are due to wear and tear of aging, to various degenerative processes, and to multiple diseases. Liability to have many diseases at the same time complicates both treatment and management.
- (b) There are many ill-understood syndromes, e.g. senile weakness, senile psychosis, senile pruritus, progressive cerebral ischaemia, nocturnal restlessness, incontinence of urine and stools, etc.
- (c) Social problems and problems of management. Emotional imbalance.

In order to understand these peculiarities, lot of study of anatomy, physiology, pathology and psychology of the old has been made all over the world. This knowledge would help in assessing ailments and finding their remedies. Thickening and calcification of arteries, thickening of valves, bradycardia, systolic hypertension, high pulse pressure, murmurs, etc. are common findings in the aged above 65 years. Three hundred thirty-five Chelsea pensioners were studied for their pulse rate and it was found that the age group 60-65 showed a mean pulse rate of 80, and those nearing eighty years showed the rate of 65. There is a general slowing of sensory and motor performance, though memory for the facts and vocabulary remain fairly constant. The capacity to learn new things gets diminished. This state of affairs has not been conclusively proved though. Speakman (1954) by observing the performance of both young and old on finding the values of stamps whose colours were assigned to different values, came to the conclusion that there was not much of difference in performance—which suggests that learning for “use” is good enough in the old. On the other hand, data (Shooter) of London tram drivers being trained as bus drivers showed that after forties they took longer to learn bus driving (3 weeks in the younger group and 4-7 weeks in the older group) and only 2/3 passed in the group above 60 years. There is loss of vibration sense and pupil reflexes as age advances. Deep jerks also diminish and it has been found that in persons above 80 years, 68 per cent have supinator jerks, 75 per cent knee jerks, and 12 per cent have their ankle jerks present. Perhaps these changes are due to changes in sensory pathways as there is not much of motor power loss in these people. Dysmetria is found in about 20 per cent of old people—with their eyes closed. Quantity of urine diminishes and so also the specific gravity. Blood urea and serum cholesterol show tendency to rise with age. 17-ketosteroids diminish in urine with advance of age. Mean heat output of the body also diminishes in old age. There has been a detailed study of pathology in the aged, and Piggott reported on 2221 post-mortem examinations of persons over the age of 65 years, and the following lesions were found in them :

*Fatal Lesions in Old Age (2221 cases)*

Myocardial degeneration .. .. .	293
Cardiovascular degeneration (atheromatous) .. .. .	148
Carcinoma of bronchus .. .. .	125
Cerebral haemorrhage .. .. .	119
Carcinoma of stomach .. .. .	110
Bronchopneumonia .. .. .	105
Carcinoma of colon and rectum .. .. .	102
Coronary thrombosis .. .. .	85
Pyelonephritis .. .. .	59
Carcinoma of oesophagus .. .. .	57
Lobar pneumonia .. .. .	56
Gastric ulcer .. .. .	52



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In the above series, 28.4 per cent died of new growth, 27 per cent of cardiovascular disease, 12.5 per cent of respiratory disease, 11.4 per cent of digestive disease, 9.2 per cent of lesions of the central nervous system, 5.1 per cent of urinary tract disease, and 5.4 per cent of miscellaneous causes.

A detailed study of aging of cells, of their components and of various organs has been made. Cowdry (1952) classified the various cells in the body in four groups according to their aging process :

- (a) Vegetative inter-mitotics, e.g. spermatogonia, basal cells of epidermis. These cells have the shortest life.
- (b) Differentiating mitotics, e.g. erythroblasts, superficial cells of the skin.
- (c) Reverting post-mitotics. These cells on aging may die, but under certain conditions they may rejuvenate and divide also, e.g. liver, kidney, thyroid cells.
- (d) Fixed post-mitotics. Highly differentiated cells which do not divide any further. Examples — erythrocytes, leucocytes, muscle cells, nerve cells.

Various authors have studied 'senility' pigment, ceroid pigment, changes in mitochondria and Golgi region with aging.

With this prelude, it would be better to discuss newer concepts about diseases and their treatment in the aged.

*Myocardial Infarction* : Infarction could be 'silent' and the only indication of its occurring may be sudden increase in dyspnoea. At times, it may present with unusual manifestations such as vertigo, syncope and mental confusion which perhaps are sometimes due to associated cerebral arteriosclerosis and fall in blood pressure due to infarction. The mortality increases with age and Pearson (1955) has mentioned the following causes which raise the mortality : (a) 'Silent' infarction and missed diagnosis, (b) complicating bronchopneumonia, (c) common disturbances of cardiac rhythm, (d) pulmonary embolism due to frequent venous thrombosis and (d) ventricular rupture. As regards the treatment of this condition in the elderly, till recently there was good deal of controversy about giving complete bed rest. Bed rest would give rise to many complications, specially venous thrombosis and embolism. It has been now proved by cardiac catheterization (Levine, 1955) that the heart, either normal or diseased, has to work 23 per cent more in the recumbent position of the patient than when the patient is sitting in a chair with his legs stretched. Hence it would be better to treat these old patients either with myocardial infarction or congestive cardiac failure in a comfortable chair rather than in bed, unless the patients are too weak to sit or are having low blood pressure. Anticoagulants should be used with all the due precautions, to prevent further spread of thrombosis, to prevent thrombosis in leg veins and thereby pulmonary embolism. If for some reasons it is decided not to use anticoagulants, elastic stockings may be worn which would increase linear velocity of blood flow and prevent thrombosis. Antibiotics may be used to prevent infections and respiratory complications.

*Congestive Cardiac Failure* : Commoner causes of cardiac failure in the elderly are coronary arteriosclerosis, hypertension and respiratory infections. By proper control of respiratory infections, cardiac failure or its exacerbations could be avoided. The use of digitalis and mercurial diuretics gives rise to two types of toxic manifestations in the aged which should always be kept in mind while treating them. Mental disturbances develop due to hyponatraemic state brought about by salt-restricted diet, mercurial diuretics and cation-exchange resins. He becomes apathetic, gets anorexia and refuses food. He may have delusions of persecution, clouding of consciousness, delirium and coma. At times, he feels that his friends, relatives and doctors are all against him. Administration of salt orally or intravenously (saline) relieves this psychosis. The second toxic manifestation is the so called 'post-mercurial redigitalization phenomenon' wherein the patient gets nausea, vomiting, dizziness and headache after administration of mercurial diuretic when he is already digitalized. These symptoms are due to digitalis intoxication which occur as a result of increased sensitivity to digitalis due to potassium deficiency. This condition can be treated by withdrawing digitalis and giving potassium chloride orally.

*Arteriosclerosis and Hypertension* : There has been a good deal of research and study of arteriosclerosis in recent years. Without going into the details of aetiology, it could be mentioned that high fat and high cholesterol contents of diet predispose to arteriosclerosis. Diabetes mellitus, hypertension, obesity, heredity, mechanical strains, etc., also predispose to arteriosclerosis.

It is still early to discuss the role of vegetable fats, vitamin B<sub>6</sub>, sitosterol and chelating agents to prevent arteriosclerosis and further observations are anxiously awaited. Serum cholesterol does not necessarily indicate the correct state of cholesterol metabolism and even correlation between serum lipids during life and coronary atherosclerosis has not been established (Paterson et al, 1956). Arteriosclerosis may be asymptomatic or it may give rise to subjective and objective impairments. The impairments may be due to direct results of arteriosclerosis or as a secondary result of thrombosis or they may be suddenly precipitated by embolism due to proximal thrombosis. Arteriosclerotic changes in the elderly can give rise to systolic hypertension, increased pulse pressure and arteriosclerotic aneurysms. Atherosclerosis of coronary arteries, cerebral arteries and mesenteric arteries can give rise to serious episodes such as myocardial ischaemia and infarction, minor or major strokes, mental deterioration and acute abdominal emergencies. Renal atherosclerosis can give rise to renal failure. Arteriosclerotic changes in lower limbs can cause intermittent claudication, wasting of muscles, and even gangrene. Except for symptomatic treatment of these cases, no specific treatment could be suggested. The predisposing causes may be properly looked after to prevent arteriosclerosis. By now, there is a good case for taking low fat diet and perhaps even more of vegetable fat rather than animal fat—though one should not be very dogmatic yet, and more data and observations should be awaited.

It has been somewhat difficult task to define normal blood pressure and Master and his colleagues (1952) have tried to put limits to normal blood pressure which has 1.282 standard deviation for each decade and sex mean blood pressure figure. Sometimes there is a wide difference between basal blood pressure and casual blood pressure. This can occur in labile elderly hypertensives before they get established hypertension. The aetiology and treatment of hypertension in the aged are more or less the same as in other age groups, hence I would not go into the details here. It should be remembered that in the elderly there are good chances of having hypertension and arteriosclerosis together and clinical manifestations due to the same. Medical treatment and proper management of elderly hypertensives bring gratifying results and delay complications. Strict salt-free diet is at times not acceptable to the elderly and some relaxation must be given. Ganglionic blocking agents along with central sedation (say with reserpine) have produced good results. Sympathectomy is usually not favoured for the aged.

*Cerebrovascular Accidents*: Elderly people have these episodes which may be producing transient or permanent disabilities. Transient disabilities may consist of paresis or paralysis of limbs, blindness, giddiness, aphasia, fits, mental confusion, etc., which disappear in a matter of few hours either with or without any neurological signs. Apart from hypertension, cerebral ischaemia by itself may be responsible for these episodes. Ischaemia may be due to atheromatous changes in cerebral arteries, or by fall in blood pressure due to bed rest, myocardial infarction, dehydration or haemorrhage. Cerebral ischaemia of longer duration can cause permanent damage to the brain. Dizziness in the elderly is more often due to cerebral arteriosclerosis though other causes like Mènière's disease, labyrinthine lesions, cardiac arrhythmias, angina pectoris, drugs, etc. may also cause it. Alvarez (1957) has drawn attention to 'little strokes' which have unusual clinical presentations like 'acute indigestion,' loss of smell, bitter taste in mouth, sudden epigastric pain, diarrhoea, abdominal distension, difficulty in swallowing, choking, sudden loss of weight, change in personality, etc. Later on, these patients may develop Parkinsonism, dementia and pseudobulbar palsy. Aetiology of these little strokes remains unexplained and it is suggested that they may be due to occlusion of smaller arteries, or perhaps spasm of these arteries. It has now been agreed that these patients with cerebrovascular disorders should be nursed out of bed and all observers have stressed the importance of activity. Use of vasodilator drugs is to be discouraged as the subsequent general vasodilation deprives the brain of necessary amount of blood. Utility of stellate ganglion block to increase cerebral circulation has been doubted (Harmel, 1949) and the measure remains controversial. The use of hypotensive drugs when the patient has both hypertension and arteriosclerosis is also contra-indicated as lowering of blood pressure would cause cerebral ischaemia. Anticoagulants if given for 8-10 days after the stroke, would hasten the recovery. Proper early mobilisation, graduated exercises, suitable encouraging environments would also help in early rehabilitation. Plastic splints help to avoid deformities and pressure sores.

*Senile Psychosis*: It has been found that nearly 75 per cent of them have organic cause for psychosis. It may be due to cerebral or non-cerebral conditions. Cerebral causes are the same

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as discussed above. Non-cerebral conditions include chronic cor pulmonale, silent myocardial infarction, hyponatraemia due to mercurial diuretics, uraemia, urinary retention, faecal impaction, barbiturates without analgesics, and terminal stage of rheumatoid arthritis. Nocturnal restlessness with agitation and delusions at times, remains unexplained and is rather difficult to treat. Mental confusion, emotional instability, depression, weeping, at times agitation, are common features in this psychosis. After treating the underlying conditions if any, judicious use of drugs like paraldehyde, chlorpromazine, methylpentynol, meprobamate, benactyzine, reserpine, amylobarbitone may help a lot. On an average, barbiturates and bromides are not very helpful and may be avoided. If faecal impaction is there, regular weekly simple enemata may help. Recently two new measures have been suggested—4 oz of 5 per cent solution of calcium chloride given as an enema gives quick result and is not cumbersome, or a wetting agent like dioctyl sodium sulphosuccinate can be used either orally or per rectum.

**Respiratory Infections :** Chronic bronchitis is fairly common in the elderly and its incidence is more in men than women. In temperate countries, respiratory infections are more frequent during winter months. The so called chronic bronchitis may turn out to be chronic fibroid tuberculosis, bronchogenic carcinoma or bronchiectasis and the proper diagnosis should be arrived at with proper investigations. A search for aetiological factors has focussed attention on bronchial hypersensitivity in some persons, role of air pollution, geographical and seasonal factors, occupational factors and responsible bacteria and virus. By improving upon these known factors, relief or infrequency of attacks could be obtained. Unless the factors which can increase body defence against infections are known, not enough could be done for these patients. It has been suggested that smaller doses of broad spectrum antibiotics can be given to these patients for prolonged periods during the season of maximal incidence of bronchitis to prevent repeated attacks but the wisdom of doing so has been doubted due to possibilities of complications like fungus infections, staphylococcal diarrhoea and vitamin B complex deficiency. Pulmonary tuberculosis sometimes may present with general symptoms like lassitude, loss of weight, weakness, apathy and symptoms which may not be referable to chest. The usual treatment with streptomycin, P. A. S., and isoniazid produces good results though fibroid cases take longer to get better and another great advantage is that these elderly people get non-infective.

**Osteoporosis :** Osteoporosis in the elderly is common, more so when they are given bed-rest or there is lack of physical activity. Women are affected five times more than men. It has been suggested that deficiency of oestrogens which stimulate osteoblasts is responsible for this occurrence. It is the loss of bony matrix which is responsible for osteoporosis in the elderly and it may not be detected radiologically till about 30 per cent of calcium is lost from the bone. The spine and the femurs are the most affected bones. The trouble may remain asymptomatic but many patients may complain of backache and radiating pains from spine. There may be shortening of the trunk and/or kyphosis of spine, and fractures of bones affected can also occur. Management of these patients should start with prophylactic measures such as adequate physical activity, high protein diet, and at least a pint of milk a day. Hormonal treatment with androgens or oestrogens or both combined in smaller dosage prevents further urinary nitrogen excretion and loss of calcium. These hormones could be given either orally or by injection. Fractures, if any, may be treated by adequate rest, splints and proper positioning of the parts concerned. Fracture of the neck of femur may have to be often treated by resting the extremity between sand-bags. Orthopaedic measures which do not cause prolonged immobilization if resorted to are helpful. Well-fitting corset for the spine gives lot of comfort and ease.

**Contractures :** These occur due to arthritis, central nervous system lesions or prolonged rest with improper positioning of joints and extremities. There may be associated deformities of bones and trophic ulcers. Contractures could be avoided by early physical activity, proper positioning of limbs while bed-rest is being given, and physiotherapy. Once they have occurred, relaxants (e.g., 'prostigmine', 'maphensin') may be used with advantage. Diathermy to joints, faradic stimulation of muscles, and mobilization with the help of either local anaesthesia or periarticular or intra-articular anaesthetic would help a lot. Ultrasonic waves have got lytic effect on fibrous tissue and prove useful in contractures.

**Deficiency Diseases :** These are more often due to inadequate diet and occasionally due to undue dietetic restrictions say in peptic ulcer, diarrhoea, diabetes mellitus, etc. Iron deficiency can give rise to achlorhydria (Witts, 1956) and also to Plummer-Vinson syndrome which is a pre-cancerous condition. Achlorhydria is more often found in elderly as such and iron deficient

diet may increase the incidence. Due to low serum iron, iron deficiency can give rise to koilonychia, atrophic gastritis, glossitis, angular stomatitis, dysphagia, etc. 'Bachelor's scurvy' has been reported in the elderly who live alone and take deficient diet, which manifests by large bruises. Royston's sign has been described in this scurvy where one finds curled up hair as dark spots on the forearm. Protein deficiency, vitamin deficiency may all be manifested as in other patients. Adequate diet with vitamins and minerals would prevent these deficiencies.

*Peptic Ulcer* : Peptic ulcer may be there in the elderly for a number of years or there may be a short history of ailment and a comparatively large ulcer seen radiologically. Chances of hour-glass constriction of stomach due to large healed or healing ulcer, severe haemorrhage due to associated arteriosclerosis, severe anaemia due to occult gastro-intestinal haemorrhage are always more in the elderly. Elective surgery is indicated in all these cases as emergency surgery for perforation or haemorrhage has higher mortality. Davey and O'Donnell (1956) reported no deaths in a series of 30 patients who underwent partial gastrectomy—all of them being above 70 years of age. Prolonged bed-rest is to be avoided in all these patients.

*Incontinence of Urine* : It is annoying both to the patient and the relatives and many a time admission to the hospital or home for the aged is sought for this trouble. Unhappy environment either at home or hospital is fairly frequently responsible for this malady—humane approach by relatives or nursing staff would cure many of them. Movements in a chair, early activity out of bed, and cheerful optimistic surroundings would also help them. Organic diseases like cerebrovascular disorders, nervous diseases, psychosis, dementia causing incontinence should be properly looked after. The same observations made above apply to incontinence of faeces in the elderly—though its management is rather difficult. Those incontinent of urine and not responding to any of the above measures are treated on conservative lines—giving of bed-pan or bottle every two hours, condom and catheter leading to receptacle to a male patient, special bed with an opening in the centre to a female patient, etc. Drugs have not been found of much value except intramuscular administration of 5 ml of 10 per cent solution of tetraethyl ammonium chloride daily for 2-3 weeks in cases incontinent after cerebral thrombosis.

*Senile Pruritus* : Infestation (scabies, pediculosis), diabetes mellitus, chronic nephritis, malignancy, reticuloses, can all cause pruritus in the elderly but most of the cases are due to diminished sebaceous secretion in the skin. Less baths and lesser soap application would preserve the small amount of secretion and cause less itching. Nobody has yet reported on daily oil application to the skin but one feels that it could be useful in these cases. Antihistamines given orally and applied locally would give some relief. For small local areas, fractional doses of X-ray can be utilized for relief. Psychological aspects of the ailment should not be neglected.

*Social Problems and Organizing of Geriatric Services* : Illness increases with age and each illness leaves in its turn a disabled elderly. According to William Morton. "with the passing of years, friends become fewer and more feeble, relatives more distant and the needs of aging patient are greater". This brings us to the difficulties both of the relatives and the elderly. Economical aspects also have their say in the care of the aged. Various schemes and suggestions have come up to make the elderly more comfortable. On an average, most of the elderly would prefer to live with their family or even on their own, rather than in special homes or hospitals. Much will depend on the customs and approach of the society. In India, the family ties are still stronger and few would prefer to leave their respected elderlies either in a special home or hospital, unless they needed special care and treatment. British medical association in its 1946 report recommended establishment of geriatric units with the following suggested functions :

- (a) Investigation and treatment of elderly patients.
- (b) Care of senile psychiatric patients.
- (c) Rehabilitation of chronic ill, physiotherapy, occupational therapy.
- (d) Discharge and resettlement of rehabilitated patients.
- (e) Co-ordination of medical and social work.
- (f) Domiciliary help.
- (g) Advice to practitioners about the aged.
- (h) Out-patient clinics for consultation and treatment.
- (i) Research and teaching of geriatrics.

## Giant Follicular Lymphoma

A special committee of the B. M. A. in 1947 suggested three sections of geriatric department.

1. Geriatric wards in a general hospital where elderly would be investigated, treated, rehabilitated and discharged.
2. Long-stay annexes to accommodate and nurse the incurable elderly patients.
3. Residential homes for elderly patients who do not need nursing but other help.

Domiciliary care of the elderly sick is favoured and recently a mobile team has been established in Belfast which helps rehabilitation of the elderly in their homes. Home help service which may consist of cleaning, cooking, washing, shopping, etc., is not only helpful to get things done but provides also companionship and is being adopted at so many centres. Visits by a district nurse have been very helpful. Home delivered meals by various women's voluntary bodies have been a boon to many an elderly. Day hospitals, "6 weeks in and 6 weeks out" hospitalization, have also been suggested. Citizen's advice bureau for the aged could be of great help for co-ordination of these welfare activities and can always help the elderly to get out of his difficulties.

No attempt has been made to make the above report on modern concepts of geriatrics exhaustive, but salient features have been stressed and the future seems to be bright if the present scientific and sympathetic outlook on the aged continues.

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## GIANT FOLLICULAR LYMPHOMA

D. Jaganatha Reddy

*Localised Tumour in the Spleen:* Pathologists all over the globe occasionally encounter the biopsy material of lymph nodes having histologically distinct entity and the cases most often running a benign course under the title "follicular lymphoma". Follow-up of these cases has disclosed a small but significant number of them assuming a sarcomatous picture attended with poor prognosis. Amin and Sirsat report an interesting case of follicular lymphoma, localised in the spleen. The patient, a female aged 50, sought aid for swelling in the abdomen which clinically was confirmed to be splenomegaly. Splenectomy was done and the spleen weighed 1815 grams. Cut surface of the spleen presented glistening white pin head sized nodules which histologically were found to be composed of lymphocytes, lymphoblasts and reticulum cells. The authors hope that the patient had been cured since lymph nodes were not the sites of lesion but follow up alone could throw more light on the condition. The illustrations are excellent.

Russel had recorded two cases of giant follicular lymphoma localised in the spleen.

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## GLOMUS JUGULARE TUMOURS OF MIDDLE EAR—See MIDDLE EAR, GLOMUS JUGULARE TUMOURS OF

## GLUCAGON

N. Padmanabhan

Glucagon, the hyperglycaemic factor of the pancreas, otherwise called the "hyperglycaemic glycogenolytic factor" (HGF) has been extracted from the pancreas. In some species it has also been isolated from the gastrointestinal mucosa. The possibility of connective tissue or lymphatic tissue being the source of glucagon has been indicated by Rao and De<sup>2</sup> who have prepared extracts of glycogenolytic and hyperglycaemic activity from the abdominal lymph nodes, spleen and tongue of rabbit and the skin of dog.

There was indirect evidence towards the origin of the pancreatic glucagon from the silver-staining alpha cells of the islets of Langerhans. Bencoseme and Frei<sup>1</sup> have prepared extracts

without any hyperglycaemic activity from the uncinate process of the pancreas of dog which is devoid of alpha cells and thus, put forth further evidence that the alpha cells produce glucagon. Evidence has cumulated in recent years to show that such agents like synthalin A (decamethylene diguanidine hydrochloride) and sulfonylurea compounds (BZ 55 and D 860) which have got a hypoglycaemic action have no effect directly on the alpha cells. The hypoglycaemia due to synthalin A is due to the damage of the liver and the destruction of the alpha cells is only secondary to this liver damage. Synthalin A acts similar to other liver-cell poisons like phosphorus, carbon tetrachloride or chloroform. In agreement with this is the finding that synthalin A produces hypoglycaemia even in the depancreatised dog.<sup>3</sup> From these it can be concluded that no drug which has got a direct and permanent destructive effect on the alpha cells comparable to that of alloxan on beta cells has yet been found.

Glucagon has been prepared in a highly purified and crystalline state and its chemical nature established by Staub et al<sup>5</sup>. It was found to be protein in nature, but was sharply differentiated from crystalline insulin in amino acid composition. Cystine or zinc which are important constituents of crystalline insulin were found only in traces in crystalline glucagon. Zinc-free crystals of glucagon have been prepared and they are indistinguishable from crystalline zinc glucagon in their biologic activity. Whether the formation of a zinc-glucagon complex in the body is a prerequisite for the biologic activity of glucagon as suggested by Weitze et al and the physiologic significance of zinc in relation to glucagon, is not yet clear.

Cross-circulation experiments in dogs have shown that glucagon is released into the portal circulation with subnormal blood sugar levels and insulin is being released when it is above normal. The administration of pituitary growth hormone has been found to augment the release of glucagon into the portal blood.

Liver is the chief site of action of glucagon released under physiological conditions and the primary effect of this hormone is to breakdown liver glycogen to glucose. Recent studies<sup>7</sup> have also shown extra-hepatic action of glucagon on the stomach, kidney and the skin. It inhibits gastric contractions, relieves hunger and produces transient decrease in the volume and acidity of the gastric juice in man. On the renal excretion of electrolytes it produces an effect by enhancing the renal clearance of sodium, chloride, potassium and inorganic phosphate as shown by studies with  $I^{131}$  by Staub et al<sup>6</sup>. In the skin Rao and De have shown the breakdown of glycogen to glucose as in the case of liver tissue.

Glucagon is held as an 'insulin-antagonist'. It has a dual action on carbohydrate metabolism—that of mobilization of liver glycogen and augmentation of peripheral utilization of glucose.

Glucagon has been used to terminate coma in cases of schizophrenia undergoing insulin coma therapy and also in other insulin hypoglycaemic comas<sup>4</sup>.

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## GONADS

### Intersexuality

B. B. Mukherji

**Chromosomal Sexing:** Various forms of intersexuality have been recognised in recent years by means of chromosomal sex differentiation. Barr<sup>1</sup> discovered that with an XX (female) combination of sex chromosomes, a chromatin mass is found adhering to the nuclei of the epidermal cells obtained from skin biopsy while no such chromatin mass is visible with the XY (male) combination. Davidson and Smith<sup>2</sup> demonstrated that the nuclei of polymorphonuclear leucocytes in blood films may show the sexual dimorphism. Moore and Barr<sup>3</sup> reported that the cells in buccal scrapings may also be used for the purpose. Finally Carpentier et al<sup>4</sup> found that equally reliable results can be obtained by examination of the vaginal and urethral smear.

**Feminine Type of Male Pseudohermaphroditism:** A feminine type of male pseudohermaphroditism was first recognised by Goldberg and Maxwell<sup>5</sup>. Schneider et al<sup>6</sup> laid down the following criteria for its diagnosis referred to as 'intersex males with purely female external genitalia and bodily habitus'—feminine habitus, primary amenorrhoea, absence or almost

## Gonads

complete absence of axillary and pubic hair, blind vaginal pouch with absence of the cervix and intra-abdominal testes. They found 12 cases in the literature which fulfilled the criteria and reported 6 cases of their own. Two further cases have been reported by Beatty et al<sup>7</sup> and Armstrong<sup>8</sup>. The source of oestrogen in these cases is the testis. The urinary gonadotropin titre is high.

Swyer<sup>9</sup> reported two similar but not identical cases. Both patients presented as eunuchoidal 'females' complaining of primary amenorrhoea. They had normal axillary and pubic hair, little or no mammary development and normal external genitalia, except for marked enlargement of the clitoris in one. The cervix was normal and the uterus rudimentary. The urinary excretion of 17-ketosteroids was normal. The gonadotropins were diminished in one and normal in the other. The chromosomal sex as determined by blood film and skin biopsy studies was male.

**Gonadal Dysgenesis:** Grumbach and his colleagues<sup>10</sup> have studied 22 cases of 'ovarian agenesis' in the light of chromosomal sexing and found that 20 of these cases have male chromatin. They have suggested the following reasonable hypothesis to explain the 'ovarian agenesis', 'Turner's syndrome' and 'the feminine type of male pseudohermaphroditism'—removal or destruction of gonads of embryos in the sexually indeterminate stage leads to development of foetuses all of which are apparently female, the males having undergone intersexualization.

**Klinefelter's Syndrome:** This used to be regarded as a testicular failure of unknown origin developing sometime during puberty. Bradbury et al<sup>11</sup> have examined 5 cases of Klinefelter's syndrome and found chromatin-positive nuclei in the oral smear. Plunbett and Barr<sup>12</sup> found chromatin-positive nuclei in skin biopsy in one case of Klinefelter's syndrome and two cases of 'congenital testicular hypoplasia' (whose testicular biopsy corresponded with that of Klinefelter's syndrome). Other cases of female nuclear sex pattern in Klinefelter's syndrome have been reported by Jackson et al<sup>13</sup> and Witschi et al<sup>14</sup>. Grumbach et al<sup>15</sup> have found female type nuclei in 7 patients suffering from azospermia; six of these were examples of Klinefelter's syndrome while the seventh patient showed germinal cell aplasia.

This paradox has not been satisfactorily explained. Nelson<sup>16</sup> has studied the chromatin pattern for 4 years in a large number of cases in relation to sex pattern. There were 62 cases of Klinefelter's syndrome in their series of which 49 had female and 13 male nuclear sex pattern. He divides the cases of this syndrome into what he calls 'true' and 'false', the former having chromatin-positive nuclei while the latter without the chromatin mass. Nelson explains the paradox by suggesting that the medullary component of the indifferent gonad is the sole embryonic structure in the male whereas in the female there is the additional cortex which controls or inhibits the growth of male reproductive system. In Klinefelter's syndrome gonads which are to develop into ovaries, fail to progress beyond the medullary stage and form the testes. These secrete androgen or its foetal equivalent which results in the development of a male type of reproductive system. It is only at puberty that the testicular deficiency is detected. Nelson prefers to call the true cases of Klinefelter's syndrome as 'female pseudohermaphrodites with gonadal dysgenesis' and false cases as 'early testicular atrophy due to tubular fibrosis'.

## Endocrines and Abnormal Sexual Behaviour

There has been a difference of opinion regarding the aetiology of abnormal sexual behaviour. Some authorities consider it to originate from endocrine disturbance such as androgen-oestrogen imbalance while others consider it to arise from psychological maladjustment. Garrone and Mutrux<sup>17</sup> have made a careful and extensive study of 50 patients with abnormal sexual behaviour and tried to find out the evidence of suprarenal and testicular dysfunction by estimating the urinary excretion of total 17-ketosteroids and their different fractions, 3-8 - steroids, formaldehydogenic corticoids, total corticoids and 17, 21 - dihydroxy -20-ketosteroids. The excretion of these steroid metabolites did not differ, with few exceptions of doubtful significance, from that of normal persons of the corresponding ages. The authors concluded that this group of patients did not show evidence of endocrine imbalance which would explain the abnormal sexual behaviour.

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### GRANULOMA VENEREUM (INGUINALE)

K. C. Sahu

During 1955, at a venereal diseases clinic in Guntur, the total outpatient attendance was 5566 and the inpatient treatment was given to a further 538 cases ; the total number of patients treated was thus 6104. Out of these patients there were 157 cases suffering from granuloma venereum, a percentage incidence of 2.57.

Out of the 157 cases of granuloma venereum, 105 were male, 52 female. Twenty-five per cent of the patients belonged to the educated middle class like teachers, clerical workers, students, etc. ; the rest belonged to under-privileged individuals of the lower socio-economic strata of society. 89.18 per cent of the patients were between the ages of 16 to 40 years. In 63 per cent, the lesion occurred on the external genitalia only ; 11.46 per cent had the lesion on the inguinal or genito-inguinal region. One case of oral lesion, one of genito-oral and one of inguino-genito-oral lesion of granuloma venereum were seen during this study. In 19 cases there was conjugal granuloma venereum and both the partners had developed the characteristic lesions.

The incubation period varied from 5 to 180 days, with an average of about 30 days. Donovan bodies could be recovered from the lesions in many cases. Treatment with streptomycin was very effective. Three cases had spontaneous improvement which was Serma's experience at Visakhapatnam and Madras. One hundred and twenty-four cases were simultaneously found to suffer from other venereal diseases ; two cases developed carcinoma in addition. Majority of the patients received 20 to 50 g of streptomycin.

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**GRANULOMATOUS LESIONS IN BONE MARROW—See BONE MARROW, GRANULOMATOUS LESIONS IN**

**GYNAECOLOGY, VENEREAL DISEASES IN—See VENEREAL DISEASES IN GYNAECOLOGY**

### HABITUAL ABORTION, AN OPERATION FOR

V. N. Shirodkar

The problem of habitual abortion has attracted the attention of obstetricians and gynaecologists in recent years. The sphincter mechanism of the internal os was studied by Keiffer and Palmer. Lisse and Asplund studied the width of the internal os in 1946. In the year 1948, I had several cases of habitual abortion occurring in the second trimester. Some of them had as many as eleven abortions between the fifth and the sixth months. One could observe in these patients a gradual yielding of the cervical canal presenting the membranes but without any show or labour pains. A few days before the abortion would take place, a copious mucoid discharge was complained of by many of them. In spite of treatment with complete rest, sedatives and hormones right from the early months of pregnancy, abortion could not be prevented. This made me think of a purely passive dilatation of the cervix under the effect of a rising intrauterine pressure. That a weak cervical musculature was responsible for abortions had come home to me by following the cases of pregnancy in women who had Fothergill operation done on them.

*What are the possible causes of this incompetence of the internal os ?* 1. Heredity has some bearing. Two of my patients are sisters. One had a history of eleven abortions and the other



## Habitual Abortion, an Operation for

seven. 2. Forceful dilatation of the cervix was the factor responsible in some of my cases of habitual abortion. 3. The dilating capacity of the cervix varies in different individuals. In some, even one normal labour is followed by habitual abortions following injury to the internal os. Forceps delivery may injure the cervix in some cases. A precipitate labour may also cause damage to it.

*How could the incompetence be diagnosed with precision?* The only certain way is to follow a case during the given period of gestation when abortions occur in a particular individual. Examine the cervical canal once a week and feel for the gradual opening of the internal os. The next best way is to get a characteristic history of more than three abortions having occurred between the completion of the fourth month and the seventh month. Even in such cases it is worthwhile following the case between these months. The history that the bag ruptures first is taken by some as a characteristic sign. I do not fully subscribe to such a view. The bag has to rupture in the majority of ordinary abortions.

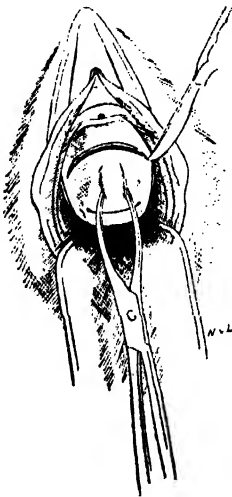


FIG. 1. Anterior incision

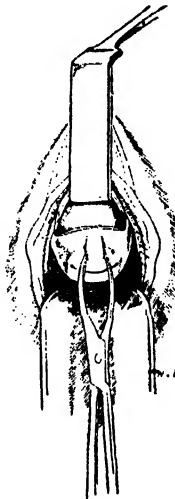


FIG. 2. Bladder and anterior vaginal wall retracted upwards to expose the internal os.

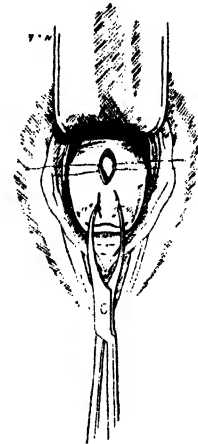


FIG. 3. Posterior vertical incision  $\frac{1}{2}$ " long.



FIG. 4. Shirodkar needle  
Right and Left.

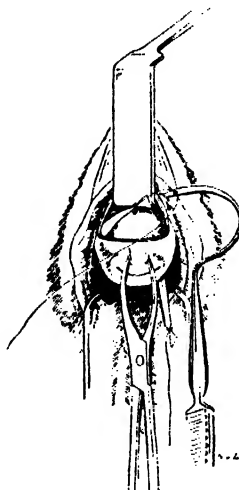


FIG. 5. One end of fascia  
pulled forward.

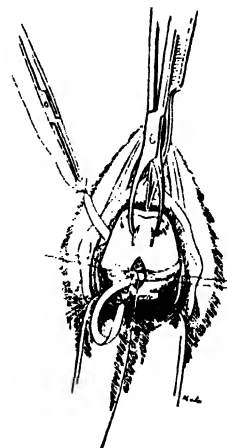


FIG. 6.

Palmer and Lash allow the patients to undergo the abortion first and then discover a weakness in the anterior wall of the isthmus. Lash describes it as a herniation of the anterior wall. Since I have operated on fifty cases during pregnancy and not seen any herniation of the anterior wall, I am not in agreement with Lash. I feel that the weakness is all round and not confined to any one part.

Some obstetricians consider that they can diagnose the incompetence in the nonpregnant state by passing a no. 9 Hegar's dilator without meeting with any resistance. I differ from this observation as this sign may be present in many multiparae. Similarly, some workers put in an opaque balloon inside the cervical canal and take X-ray pictures which show dilatation of the internal os. To my mind, such an appearance is not a reliable guide.

Recently, Dr. Bergman of Malmo, Sweden, has devised a rubber balloon attached to a manometer. He passes the balloon into the uterine cavity and as it is being pulled out past the internal os, he notes down the rise in pressure. A lack of rise in the pressure is regarded as a sign of incompetence. I am not convinced as to how these findings in the nonpregnant state can give information about the state of the os in the softened pregnant uterus. Bergman probably assumes that if the os is weak in a non-pregnant state then it is still weaker during pregnancy. I hope that this test will prove as precise as direct observations of the state of the os during the critical period by frequent internal examinations.

*When do I operate on these cases?* In a clear-cut case I would like to operate during the nonpregnant period as the operation is easy and one gets plenty of time to get the fascial ends to unite by sound and firm adhesions. During pregnancy, I prefer to operate within the first four months as the operation is comparatively easy and the vaginal walls are not so friable or excessively vascular. I have carried out the operation as late as the 27th week of pregnancy. The first case operated in this manner was in 1949. I used to dissect the vaginal walls away from the cervix, by making a circular incision round the cervicovaginal junction. The region of the internal os and isthmus uteri were well exposed. Then I used to encircle this part with three purse-string sutures one below the other. I used chromic catgut no. 2. I soon found that catgut did not last very long and there were many failures. I subsequently decided to use a strip of fascia lata and I have not regretted it since.

The operation is carried out as follows:

1. At the outset, a strip of fascia lata five inches long and  $\frac{3}{4}$  inch broad, is removed and each end of it is transfixed with a linen suture, the ends of which are left long.
2. An incision is made in front of the cervix about the level of the internal os, as in an operation for anterior colporrhaphy (Fig. 1).
3. The anterior vaginal wall and the bladder are pushed up away from the cervix and held up with a retractor (Fig. 2).
4. The cervix is pulled forwards, and a small vertical incision is made on the posterior cervicovaginal junction (Fig. 3).
5. A special aneurysm needle (Fig. 4) is passed through the right corner of the retracted anterior incision and made to pass retrovaginally clinging to the side of the cervix till it emerges through the posterior incision (Fig. 3).
6. One end of the strip of fascia lata is engaged in the eye of the aneurysm needle and is then drawn forwards (Fig. 5).
7. The same steps are repeated through the left angle of the anterior incision (Fig. 6, 7.)
8. Hold the two ends of the fascial strip and make a reef knot with it, tight enough to fit snugly round the internal os. Fix the knot with linen sutures. It is better to fix the first loop of the knot at first and then finish the second loop and fix the whole knot again. The two ends of the strip are individually fixed again to the encircling portion of the strip (Fig. 8 a.)

Formerly, I used to hold the two fascial ends parallel to each other and fix them to the cervix by three separate sutures. These used to slip through the knots (Fig. 8.)

9. The anterior and posterior incisions are now closed with catgut sutures (Fig. 9, 10).

It is better to inject 0.5 c.cm adrenaline in 10 c.cm of distilled water or saline all round the fornices ten minutes before operating on pregnant women. I use 0.75 c.cm of heavy nupercaine for the spinal anaesthesia. If one wishes to make the patient unconscious, she may have gas

## Habitual Abortion, an Operation for

and oxygen. One should not give pentothal if the patient is given adrenaline. Two patients under my care had severe fall of blood pressure with such a combination.

If the two ends of the fascial strip are not tied to each other firmly, they might slip between the knots as pregnancy advances and a premature labour may result. Even after this operation, comparative rest is essential in the last two months, and a fortnightly examination, to note the condition of the cervical canal is recommended. If the cervix is opening then the patient should be put to bed for the remaining period. It is better to put a reef knot on the fascia in front of the cervix and then stitch the knot and the two ends to the main fascia encircling the cervix.

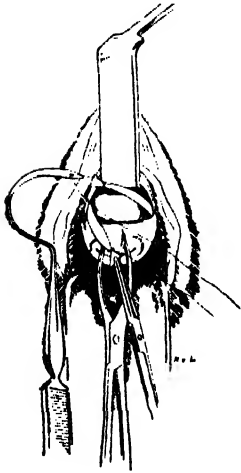


FIG. 7. The other end pulled forward.

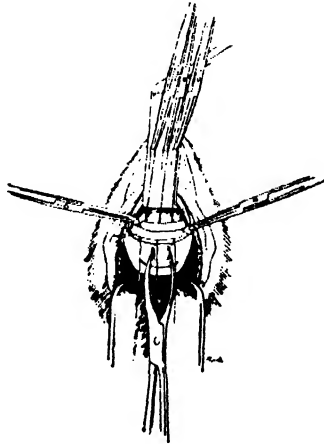


FIG. 8.

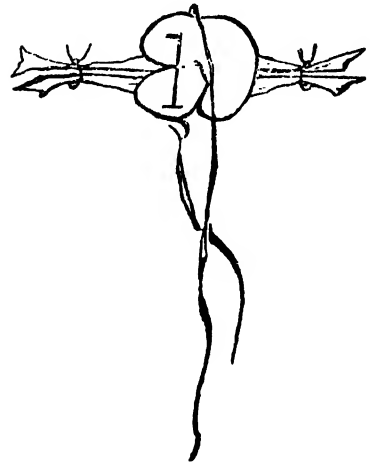


FIG. 8a. Reef knot transfixed with linen suture.

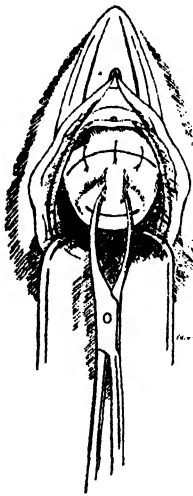


FIG. 9. Closure of anterior incision



FIG. 10. Closure of posterior incision.

So far 80 cases have been operated by me in this manner ; fifty of them during pregnancy and 30 nonpregnant. Of the fifty, 80 per cent have been delivered at or near term by caesarean section. Out of the 30 done in nonpregnant state, ten have become pregnant and all delivered by caesarean section at term. It is better to operate when the patients are not pregnant as the operation is easier and the vaginal walls less friable.

## HAEMOGLOBINS

A. Sitaramamurti

**Normal Haemoglobins :** Investigations of the dissociation of oxyhaemoglobin in birds by Hall (1934) and Rostorfer and Rigdon (1946) led to the suggestion that there are two normal haemoglobins, one embryonic or foetal and the other an adult form. Ever since, such differences were also noticed in mammalian species as well (Lecks and Wolman, 1957). Johnson and Dunlap (1955), with experiments on chicken observed the two haemoglobins in each age group tested and the fast moving component, the  $\alpha$ - haemoglobin, appeared to be in lower concentration than the slower moving  $\beta$ -haemoglobin component. The migration was towards the anode. The results were 30 per cent  $\alpha$ -Hb and 70 per cent  $\beta$ -Hb in the embryo and 20 per cent  $\alpha$ -Hb and 80 per cent  $\beta$ -Hb in the adult. In the mammals the presence of adult Hb in the embryo may be explainable as due to the placental transfer mechanism but in the absence of such a mechanism in birds, the presence of the adult Hb in the avian embryo is not easily explainable and may require further experimental work. Saha et al (1957) state that they observed only one component, Hb A, in mammals and two components, Hb A and HbF, in avians.

Chromatographic separations of different carboxyhaemoglobins by Prins and Hensman (1955) and of the carboxyhaemoglobins of different species by Broadman and Partridge (1953) have been reported. The application of column chromatography to oxy-Hb has shown that not only different types of Hb can be separated, but also, that the normal adult Hb itself can be resolved into at least three components. Morrison and Cook (1955) gave the first indication of the separation of undenatured normal adult Hb into various fractions and they indicate the non-homogeneity of normal adult Hb and for the separation of the distinct molecular species by employing suitable chromatographic system, they recommend using the ionic exchange resin I R C-50.

**Abnormal Haemoglobins :** Up till now, there appears to be nine different haemoglobins in addition to type A (adult) and F (foetal) which may be identified by their physiological characteristics. These haemoglobins have been designated in order of their discovery as S, C, D, E, G, H, I, J and K (S was once labelled as B) by the names of the alphabet. The occurrence of the clinical syndromes associated with haemoglobins SC, SD, EE and GG, and with haemoglobins SC, SD and SA, as well as other combinations of haemoglobin S thalassemia have been described. The knowledge concerning the inherited abnormality of human haemoglobin is rapidly expanding and interesting questions regarding the genetic, biochemical and clinical relationships of the genes are being posed. As a result of studies in which two or more of the genes are responsible for the abnormalities in haemoglobin functions simultaneously, it has been noted (Schwartz et al, 1957) that the genes responsible for the haemoglobins C and S are probably alleles and the genetic factor involved in the production of these two types of abnormal haemoglobins is independent of the thalassemia factor. Studies have not so far progressed concerning the genetic relationships of the genes responsible for haemoglobins D, E, G, H, I and J to one another and to the above mentioned genes. Schwartz and his co-workers (vide supra) studying a Caucasian family, postulated that the genes responsible for haemoglobins S and G and for the thalassemia defect are present and that the genes responsible for Hb G and Hb S cannot be alleles and the genes responsible for Hb G and thalassemia cannot be alleles and that the Hb G should probably be regarded as a normal variant of Hb rather than an abnormal type of Hb. Singer and his co-workers (1957) reported a family study in which simultaneous presence of C thalassemia and S thalassemia diseases were noticed with marked interaction of the genes and they state that the Hb S plus F pattern cannot be any longer assumed as diagnostic of sickle cell anaemia and evaluation of all haematological data and the family background of the patient may be necessary to rule out the presence of thalassemia gene. Jensen et al (1957) have given an account of a patient with homozygous haemoglobin C disease and the diagnosis in all patients was established by the characteristic electrophoretic patterns of abnormal haemoglobins.

Hb E has been encountered in three combinations (Nakorn & Minnich 1957)—(1) As a heterozygous form in combination with normal adult Hb; (2) In association with thalassemia gene and (3) In homozygous state. They have reported about an unusual family in which the father may have been heterozygous for both the Hb E and the thalassemia gene while the mother was homozygous for Hb E. These two genetically determined abnormalities being carried on separate genes some of their children might have previously unrecognised thalassemia homozygous Hb E disease as well as thalassemia heterozygous Hb E disorder. Recommenda-

## Haemorrhage, Accidental

tions were made for gene symbols for the various thalassemia haemoglobin combinations but have not yet been decided upon for the three chief genetic combinations, namely 1. Thalassemia-heterozygous Hb E, or 2. Thalassemia-homozygous Hb E or 3. Homozygous Hb E. In the ten members of the unusual family studied, they found that the mother and four of the children were homozygous Hb E disease, the father and the three children either thalassemia-heterozygous Hb E or thalassemia homozygous Hb E disease and in one boy, a definite diagnosis could not be made. Chatterjea et al (1956) state that they observed two cases of Hb E homozygote, 25 cases of Hb E heterozygote and 26 cases thalassemia Hb E heterozygote in a survey of 700 subjects. Chatterjea and co-workers (1956, 1957) have found that thalassemia is fairly common in Bengal (India). More than 200 patients with their families were investigated for clinical, biochemical, haematological and genetic aspects and a large number of them happen to represent Hb E thalassemia disease. Thalassemia as also Hb E have been found separately in heterozygous state. The mode of inheritance is being studied (Chatterjea, 1957). A case of Hb S thalassemia disease was also recorded recently in a Bengalee child.

Bird and Lehman (1956) mentioned that in India, sickle cells have been seen in some isolated aboriginal populations; haemoglobin C has never been found and instances of thalassemia have been reported from India.

An international symposium for discussing the various aspects of "abnormal haemoglobins" was held at Istanbul, Turkey, in September 1957, under the auspices of the Council of International Organisations of Medical Sciences which was created by the WHO and the UNESCO. The main heads under which the symposium was held for discussion included, (1) the identification of haemoglobins, (2) the haematological aspects of haemoglobinopathies (3) The genetic control of haemoglobin production and (4) the geographical distribution of the haemoglobins. The proceedings when published may be very valuable for workers in this field.

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## HAEMORRHAGE, ACCIDENTAL

K. Bhasker Rao

In one third of the antepartum bleeders, the cause is accidental haemorrhage. It is seen more in nontoxic group than in the toxæmic individuals contrary to previous teaching. In a large series of 398 cases over 22 years Douglas<sup>1</sup> found that only 19 per cent had toxæmia. In Macafee's<sup>2</sup> experience of 360 cases over 9 years it was 31.9 per cent. Accidental haemorrhage is an important cause of prematurity. The foetal mortality varies from 20 per cent to 60 per cent but maternal death rate is only 5 out of 398 patients. Important complications are afibrinogenaemia and renal cortical necrosis. Both these conditions may result if the interval between the onset of uteroplacental apoplexy and delivery increases to 4 to 6 hours. The renal cortical necrosis is a serious condition and if oliguria or anuria should persist in these cases for over six hours, irreversible kidney changes occur and survival becomes difficult.

The trend in treatment in accidental haemorrhage is more towards caesarean section (40 per cent of cases). It improves the foetal salvage rate and reduces maternal complications.

When a conservative method of artificial rupture of membranes and pitocin drip, fails and the bleeding is persistent or labour is at a standstill, caesarean section is done. It is also indicated when the uterus becomes tender and more tender indicating internal haemorrhage, when the fibrinogen level falls to 100 mg per cent or below, in persistent oliguria or anuria for over 2 to 3 hours and in mild cases with foetal distress when the foetus is more than 2000 g. The Couve-laïre uterus is seen in about 75 per cent of cases where delivery is delayed for more than 3 hours after placental separation; but "no matter how black or damaged the uterus may look, it will contract" and it is unnecessary to remove it if the clotting defect is controlled (Barry)<sup>3</sup>. Marginal separation of the placenta with rupture of the veins and resultant haemorrhage is seen in 1/5 of the cases but there is no associated retroplacental haematoma. In this type of accidental haemorrhage foetal mortality is low.

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#### HEART DISEASE IN PREGNANCY—See PREGNANCY AND HEART DISEASE

#### HEART, PHYSIOLOGY OF

R. K. Pal

By electrical records taken from the region of the pace-maker in the right auricle and from the tip of the left auricle, Marshall and Vaughan Williams (1956)<sup>11</sup> have shown that the pace-maker region is able to resist cooling to a temperature several degrees below that at which rest of the auricle ceases to contract and the link between the pace-maker and the surrounding tissues thus broken by cooling can be restored by acetyl choline. Vaughan Williams (1955)<sup>16</sup> by studying in details the effects of different ions and changes in pH after perfusing isolated rabbit's heart was of opinion that 'if the conduction velocity is a direct function of the rate of entry of Na ions and the force of contraction an inverse function of the rate of exit of the K ions the association of increased conduction velocity with increased CO<sub>2</sub> and decreased conduction with acid extracellular pH, might both be explained by the hypothesis that cations moved more rapidly than usual towards the side of the membrane whose pH had been changed in the direction of acidity'. Hercus, McDowall and Mendel (1955)<sup>9</sup>, on the other hand, have shown that the heart preparation when placed in a bath of normal Krebs solution takes up sodium and loses potassium, but stretching the muscle increases sodium extrusion whereas anoxia increases the uptake of Na and also produces sustained damage to the Na extrusion mechanism. Stimulation of anoxic muscle increases the Na uptake but not that of normal muscle which can extrude sodium efficiently. The beneficial effects of reducing the Na in the bath during the depression produced by anoxia or rapid stimulation of the isolated right ventricular muscle of rat suggest that the depression is produced by the uptake of sodium (McDowall et al<sup>12</sup>, 1955). Kahali and Bhargava (1956)<sup>10</sup>, again after perfusing frog's heart with modified Ringer solution showed that sodium chloride was essential not only for maintaining the osmotic pressure but also for the excitability of the cardiac muscle and consequent to the reduction of sodium chloride the heart showed better contraction when isotonicity was maintained by addition of sucrose to the perfusion fluid.

Trounce (1955)<sup>15</sup> has shown that an aminosteroid, dimethyl epidehydro-androsterone malleate (Compound 358) in the isolated perfused rabbit's heart produced diminished contraction of both auricles and ventricles when amounts varying from 0.5 to 2 mg were added to the perfusion fluid. In the intact animal i. v. injection of 60 mg within one minute of the injection showed effects like quinidine, starting with slowing of heart and bundle branch block, then interventricular block and finally bizarre ventricular complexes (as shown by the E. C. G.) ultimately ending in death. Similar effects were also obtained with synthetic steroid amines on heart by Gould, Shapiro and Hirshberg (1954)<sup>7</sup>. Rindani and Chavan (1955)<sup>13</sup> too, showed that both cortisone and DOCA caused an inhibition of contraction in the perfused isolated frog's heart while progesterone was without any effect.

Weidman (1955)<sup>18</sup> measured the membrane potential of a single Purkinje's fibre (calf or sheep) by means of an intracellular microelectrode and found that a fourfold decrease or increase in the extracellular fluid (Tyrode's) had no marked effect on the (1) size and shape of action potential, (2) value of maximal diastolic membrane potential and (3) membrane resistance.

## Heart, Physiology of

Much more depolarisation was required to excite a fibre in solutions rich in calcium and less depolarisation in solutions lacking in calcium, which account for the stabilizing effect of Ca ions. The fibrillation produced in the presence of cholinesterase, an inhibitor of acetyl choline, continued for a few minutes after cessation of the stimulation, the length of time being greater according to concentration.

*The Cardiac Reflexes* : The various changes that take place in the heart rate in dogs anaesthetized with morphine, dial, urethane and sodium phenobarbital, do not appear to be related to any alteration in arterial blood pressure or respiration and cannot be explained entirely by reference to simultaneous changes in the mean right atrial pressure (increased with reference to atmospheric pressure) but rather appear to be related to initial low heart rate and conversely slowing takes place if the initial rate is high (Coleridge and Linden, 1955)<sup>1</sup>.

Douglas, Ritchie and Schawmann (1956)<sup>4</sup> showed that when stimulation of the aortic nerves in rabbits is prolonged sufficiently to cause a maintained depressor response, it is usually independent of the pattern stimulation and only at the low rates of stimulation is the interrupted type slightly effective. The relationship between the depressor responses and the frequency of stimulation remained substantially the same whether determined with brief periods of stimulation (2-16 sec.) producing transient responses or with a long lasting stimulation producing maintained responses.

Evans and Murray (1954)<sup>5</sup> are of opinion that of the two types of fibres in the aortic nerve the nonmedullated afferents (C fibres) far outnumber the medullated afferent depressor fibres (A fibres). According to Douglas and Schawmann (1956)<sup>4</sup> the former have powerful depressor activity but produce the reflex depressor effects at much lower frequencies of stimulation than the A fibres. A single shock which excites the non-medullated C fibres often produces a depressor response. A summation of the reflex effects of two such shocks occurs when the interval between them is 4-2000 msec., and it is maximal when the interval is between 60 and 250 msec.

Afferent vagal fibres with characteristic discharge for cardiac atrial stretch fibres (sensitive to variations in the circulating blood volume) have been found by Gaur et al (1954)<sup>6</sup> and isolated in the dog. But Hewey and Pearce (1956)<sup>5</sup> working with cats confirm that the receptors lie in the atrium or in the pulmonary vein near the mouth as there is increase in the activity of such fibres from the left atrium on distension and the absence of any adequate activity during partial obstruction of the pulmonary veins. The absence of discharge in the fibres during atrial systole when the pressure is greatest and the close relation of the peak discharge to maximum atrial filling in late diastole when the volume is greatest, support the conclusion that the receptors respond to stretch rather than to pressure. So probably, cardiac stretch receptors serve as one sensory mechanism in a reflex regulation of blood volume by control of urine output. The position of these receptors was located in the atriovenous tissues on the right and left side of the heart of dog by Coleridge et al (1957)<sup>2</sup>, by occluding vessels and inducing local changes of blood pressure in the chambers of the heart and in the great vessels which altered the discharge in a single vagal fibre to find approximately the position first and then accurately by punctate stimulation of the endocardial surface after opening the heart. Such receptors on histological examination were found to have characteristic end-formations which are situated in the endocardium and junctional tissues of the right atrium, venae cavae, and pulmonary veins and left atrium, with branching of myelinated fibres, 3-10 $\mu$  in diameter, forming a plate parallel to the endocardial surface. A few end-formations were also seen in the posterior part of the atrial septum but no receptors were located there by punctate stimulation. The cardioaccelerator fibres have been demonstrated by Waites (1957)<sup>17</sup> in the lower course of the right cervical sympathetic nerve of sheep, which are mostly preganglionic to the right stellate ganglion but also sometimes contain a small post-ganglionic component. There is no evidence of their presence in the upper half of the right or in any part of the left cervical sympathetic nerves. The cardio-accelerator fibres of the neck come from the thorax through the limbs of the ansa subclavia and ascend in the right sympathetic, returning to the thorax in the same nerve; their further course between the cervical sympathetic and heart is variable.

Electrical stimulation of the carotid sinus nerve causes a fall in the systemic blood pressure, slowing of the heart rate and a fall in the pulmonary arterial pressure. The depressor response is augmented however, by section of the contralateral sinus nerve or both cervical vago-sympathetic nerves, which according to deBurgh Daly and Schweitzer (1956)<sup>3</sup> is due to

diminished buffering effect of the sinoaortic nerves. Robertson, Swan and Witheridge (1956)<sup>14</sup> have shown that inhalation of ether, chloroform or trichloroethylene results in an increase in the sensitivity of the carotid and aortic baroreceptors. The receptors in the perfused carotid sinus also show an increased discharge in conditions in which contraction of the smooth muscle of the arterial wall occurs.

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#### HAEMOPHILIA, TREATMENT OF

R. Subramaniam

The therapeutic management of a severe case of classical haemophilia has changed but little in the last 20 years. The systematic treatment of haemophilia consists entirely in the use of sufficient quantity of plasma to maintain a high enough concentration of the anti-haemophilic factor (A.H.F.) in the patient's blood so that a normal process of haemostasis and healing occurs. The amount of plasma and the duration of the treatment naturally depend upon the location of haemorrhage and its response to treatment. As far as possible, fresh, freshly frozen, or freshly lyophilized plasma is to be used. In an emergency a freshly available plasma or a blood bank may be utilised. The loss of A.H.F. factor in citrated blood is less than that in the oxalated plasma. It was felt that the use of fraction I of Cohn did not offer any specific advantage. On theoretical grounds A.H.F. level in the patient's blood should be approximately 30 per cent of normal but in practice a much smaller percentage is enough. But when a smaller amount is used, the clinician should be prepared to meet with failure. Whenever there is not much loss of blood as in bleeding occurring in a joint cavity, absorption of the haemorrhage is helped by it and restoration of normal function is aided; where haemorrhage is subcutaneous it may be left untreated; where evacuation is contemplated plasma transfusion may be given. In evacuating a joint cavity hyaluronidase facilitates evacuation. Energetic treatment is called for in the younger age groups but in the older age groups rest and analgesics work equally well. As a rule, haemophiloid patients are better treated in a hospital or in an institution where a team of resident physicians and fresh blood and fresh plasma are available. The use of fresh blood or plasma does not mean one can avoid local haemostatic agents like thrombin, thromboplastin, and Russell viper venom for accessible external bleeding though these are admittedly of poor value in treating large wounds. Repeated transfusion may result in the development of "auto-immune" anticoagulants. It is not possible to completely avoid this though one may hope to control it to some extent by avoiding transfusion at frequent intervals or postponing the transfusion till it becomes very necessary and using steroid hormones instead. In between the bleeding episodes, good diet with plenty of vit. C with avoidance of upper respiratory infections, and particularly of injuries. It has been suggested that large transfusions may dilute and neutralize the anticoagulants in the body. It has been pointed out that the clot-promoting activity of infused blood or plasma are short-lived, disappearing in the course of 24 hours after the transfusion.

With regard to the treatment in between the episodes of bleeding, it was felt that it may be even risky to administer blood or plasma or plasma fractions as a routine. It was even felt that it was a dangerous procedure that a person may be sensitized and in a serious situation



## Hepatic Coma and Alimentary Intoxication

it may not be possible to save the patient even by fresh plasma or by transfusion of fresh blood. If there is anaemia, fresh blood is of value whereas in cases with no anaemia, fresh plasma is adequate. It has also been felt that in between the bleeding episodes the patient should be educated about the disease so that he will do his best to avoid getting injuries and would also know how to look after himself. It was suggested on theoretical grounds that total exchange transfusion should be tried though it does not seem to have been tried by any of the panel members. Besides blood, vit. K 10 mg and vit. C 200 mg daily orally was advised. With regard to haemophilia B where there is a deficiency of platelet co-factor, though the general treatment may be in a manner as already outlined, whole blood transfusion may give more dramatic results than in the treatment of haemophilia A and the effect of the transfusion may be expected to last 7 or more days. It is felt that haemophilia still remains a challenge to the haematologists and the development of refined bovine plasma may offer a solution, although the problem of antigenecity remains to be solved.

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## HEPATIC COMA AND ALIMENTARY INTOXICATION

V. Iswariah

The hand of alimentary toxæmia or 'auto-intoxication' has made a full circle and medicine is back again to take serious cognizance of this factor in hepatic coma.

Experimentally, in dogs with Eck's fistula, ingestion of large amounts of protein led to drowsiness, mental disturbances and coma<sup>2</sup>. Clinically it is also noticed that patients with cirrhosis of the liver with ascites, when treated with ammonium chloride and mercurials, go in for early coma. These and other observations had led to the surmise first that the blood level of the ammonium ion determined the onset and continuation of coma<sup>5</sup>. In cirrhosis, high ammonia level in blood could also be traced to collateral circulation and impaired liver functions<sup>9</sup>.

Sometimes ammonia was also increased in C.S.F. with associated neurological complications<sup>8</sup>. To bind the offending ammonia, large amounts of glutamic acid were administered as suggested by Walshe<sup>7</sup> but the results were not unequivocal.

Study from another angle by Challenger and Walshe<sup>1</sup> also directed to similar presumptions. They had isolated two compounds methyl mercaptan and dimethyldisulphide from the urine of patients with hepatic coma with factor hepaticus. The presumed source of these is methionine. The oxidation product of methionine is said to prevent formation of glutamine from ammonia and glutamic acid, all these upsets being ultimately traceable to bacterial enzymatic action in the gut.

Methionine has been in use for some time as liver protector, to prevent fatty infiltration and subsequent cirrhosis. From the above findings it looks as though there are serious hazards to methionine therapy. Sherlock et al<sup>6</sup> gave 8 to 20 g of methionine daily by mouth to patients with liver disease and noticed progressive deterioration of consciousness in nine out of 20 patients. Strange enough, intravenous methionine on the other hand was not followed by mental deterioration, in those who showed deterioration by oral route. Further, oral methionine accompanied by chlortetracycline, again did not precipitate the mental symptoms. The conclusion that one can arrive at by these findings, is that large doses of methionine release a 'toxic agent' during alimentary bacterial activity; the broad spectrum antibiotics prevent this toxic agent being released. Sherlock and her colleagues further suggest that oral administration of methionine may be a useful test to diagnose some neurological manifestations and that it would be of use in selecting cases for portocaval anastomosis. Fisher and Faloo<sup>3</sup> reported favourably on the use of broad spectrum antibiotics; they had actually noted fall in level of blood ammonia with neomycin in eight patients with cirrhosis of the liver.

Gyorgy<sup>4</sup> had observed on the other hand that antibiotics administered orally, had prevented nutritional necrosis of liver in animals.

In summarising the treatment of hepatic coma, Sherlock and her colleagues (1956) observed that restriction of protein with administration of broad spectrum antibiotics may be of value.

Intravenous sodium glutamate on 12 occasions was tried in vain. Prognosis according to them was better in cirrhosis than in acute virus hepatitis, if treatment is started in the precomatose



PLATE V

HODGKIN'S DISEASE OF THE LUNG



FIG. 1

*Reduction skiagram of the chest. Extensive opacity in the left side with fluid level.*



FIG. 2

*Photomicrograph illustrates reticular cell hyperplasia of the lung totally blotting the normal structure of the lung, (H&E x72).*

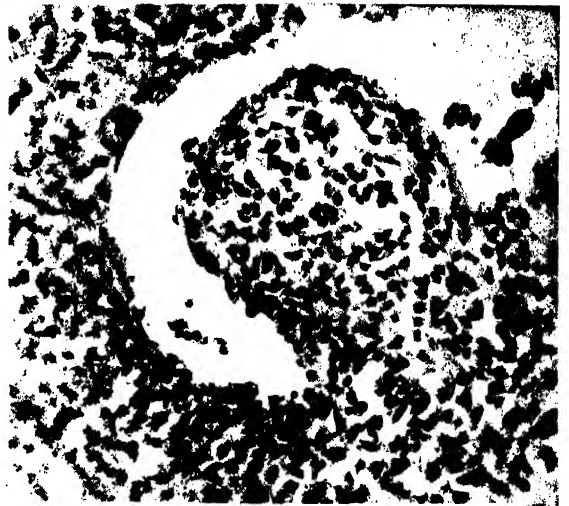


FIG. 3

*Photomicrograph is a magnification of figure 2 (H&E x324).*

## Hirschsprung's Disease (Congenital Megacolon)

stage. In cirrhosis, when coma is associated with signs of liver failure such as ascites, jaundice or a low serum albumin value, prognosis was not good. It has however to be remembered that altered liver function permitting passage of toxic products of suspected alimentary origin from nitrogenous substance to the brain is only one aspect of the problem.

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## HIRSCHSPRUNG'S DISEASE (CONGENITAL MEGACOLON)

J. B. Mehta

Hirschsprung's disease or congenital megacolon is a congenital condition in which the parasympathetic ganglion cells are absent through a variable length of the large gut. Swenson observed that the dilated loop of the colon was not the site of the primary pathology but a secondary effect of lack of peristalsis of the distal colon<sup>2</sup>. In fact this distal portion of the colon is empty of faeces, unlike in habitual constipation. It is from this portion that the parasympathetic ganglion cells are absent. Removal of this offending portion of the aganglionic colon cures the disease. The extent to which this colon is affected varies, and prognosis and ease of operative procedure vary directly with the length of the affection. In fact at operation the amount of gut to be resected will depend on frozen section microscopic examination of the colon. Though commonly the aganglionic portion ends at the sigmoid colon, it may extend even to the small intestine<sup>2</sup>.

Radiography helps in the diagnosis of the extent of the colon affected. In the lateral and oblique postures a barium enema may outline the narrowed portion. It is important to avoid injecting too much of barium so as not to obscure the picture by dilated loops.

It is not generally appreciated that the disease may prove fatal even in the adolescent. In newborn infants it has to be distinguished from that due to meconium ileus.

In India surgical treatment on the present concept has been reported by Sulakhe<sup>1</sup>.

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## HODGKIN'S DISEASE OF THE LUNG

D. Jaganatha Reddy

Reports of primary lymphoma of the lung occasionally appear in medical literature. Although many doubt the real occurrence of primary Hodgkin's disease of the lung, authentic reports of the same confirmed at necropsy are not wanting. Reddy et al recently reviewed the literature on the subject and reported an interesting case.

A 50 years old male patient attended the Government General Hospital at Guntur, for dyspnoea, cough with expectoration of six months' duration, associated with hoarseness of voice. The trachea was deviated to the right. Axillary and inguinal lymph nodes were enlarged. The left half of the chest was stony dull on percussion. The total white cell count was 20,000 per c. mm with 80 per cent neutrophils. V. D. R. L. test was positive. Skiagram of the chest showed opacity in the left half of the chest ; right border of the heart was one inch lateral to the right sternal border and the trachea was deviated to the right ; a dense mediastinal shadow was present (Fig. 1). The patient expired.

At autopsy, massive enlargement of lymph nodes in the anterior mediastinum covering the pericardium was observed. The upper half of the left lung was composed of soft white and homogenous tumour tissue and was adherent to the parietes. Cavitation in the tumour mass was seen, signifying necrosis. Studded over the pericardium, the great vessels and the myocardium, the tumour nodules and the neoplastic tissue enveloped the structures in the posterior mediastinum. Lymph nodes in the axilla and inguinal regions were enlarged. Sections of the tumour mass of the lung showed replacement of the architecture of the lung by reticular cell hyperplasia—the cells were of primitive type—varying in size and shape with deeply-staining nuclei. The tumour cells invaginating into the alveoli was a significant feature (Figs. 2 and 3). Perivascular accumulations of these cells, necrosis and

## Hormones, Steroid

haemorrhage were encountered. The pleura, oesophagus, aorta and vertebrae were infiltrated by the tumour cells. The inguinal lymph nodes presented typical Sternberg giant cells characteristic of Hodgkin's disease. The picture was one of exclusive reticular cell hyperplasia unmingled with plasma, round or eosinophil cells, all confirming Hodgkin's sarcoma. The authors suggest that the neoplastic process *de novo* arose from the lungs and that lymph node biopsy of supraclavicular group of glands or elsewhere may offer a clue to visceral Hodgkin's disease and the possibility of multicentric origin of the neoplastic process should not be lost sight of.

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## HORMONES, STEROID

T. S. Row

Though cortisone, prednisone and prednisolone are the steroids used in therapeutics, it is hydrocortisone which is the naturally occurring hormone in the body. Cortisone, prednisone and prednisolone are converted in the liver to hydrocortisone.

The adrenal cortex secretes hydrocortisone which flows into the adrenal veins; hydrocortisone is constantly being degraded in the body into tetra-hydrocortisone, and tetra-hydro-hydrocortisone which is excreted in the urine after being conjugated with glycuronic acid. A balance is struck in the production of the hormone and its destruction, so that the blood plasma concentration of the hormone lies between 3 to 15 mg per 100 ml.

Stress calls forth an increased secretion of the hormone. Fractures, surgical operations and other trauma, painful conditions as coronary thrombosis, severe infections, are all attended with increased hydrocortisone production. It is not certain whether in these conditions there is an increased utilisation of the hormone by the tissues. It is also not known if there is an increased need for the hormone. All we know is that persons with hypofunctioning adrenals can stand such conditions of stress poorly.

Adrenal cortical activity is controlled by the anterior lobe of the pituitary through production of its adrenocorticotrophic hormone (ACTH). A self regulating mechanism exists between the pituitary ACTH secretion and secretion of hydrocortisone by the adrenal cortex. ACTH stimulates hydrocortisone secretion; increased hydrocortisone blood level in its turn tends to diminish ACTH secretion by the anterior pituitary. The aim of corticosteroid therapy is to provide a raised hydrocortisone blood level. This could be achieved by administration of ACTH in a person with normal function of the adrenal gland, or by administration of cortisone, prednisone or prednisolone.

Administration of cortisone or hydrocortisone over long periods will suppress normal production of ACTH, leading to adrenal cortical atrophy. This by itself, during administration of steroids, is immaterial, but should the treatment be stopped suddenly the dormant adrenals may not be able to resume normal function, with the result that serious adrenal cortical deficiency may occur. This must always be kept in mind when prolonged steroid therapy is contemplated. This withdrawal form of acute adrenal insufficiency can be prevented by gradual tapering off of steroid therapy or under cover of ACTH.

Corticosteroids should be used with great caution, always keeping in mind the adverse effects that may arise. Hydrocortisone tends to inhibit natural tissue reactions of inflammation and repair, delay wound healing, and reduce the natural resistance to bacterial infections. These compounds do not cure any disease process but they suppress unpleasant manifestations as long as they are in use, these return with the withdrawal of the drug, unless a spontaneous remission has occurred in the meanwhile.

The possible complications during therapy are as below:

1. There may be oedema due to salt retention, a latent cardiac failure may be aggravated. A record of the body weight should be kept and the jugular venous pressure watched; restriction of sodium intake is a useful preventive measure. Frank congestive failure not responding to the usual line of treatment is a definite contraindication to the use of cortisone or hydrocortisone.

2. Potassium excretion: This may result in severe hypokalaemia with alkalosis and is likely to be more pronounced in ulcerative colitis. Potassium chloride in daily doses of 3 to 5 grams should be administered during long-term corticosteroid therapy.

3. There may be glycosuria, a latent diabetes may be brought to light, an established one aggravated.

4. Features akin to Cushing's syndrome, as development of moon face, cutaneous striae, acne, hirsutism, etc. may occur.

5. Mental changes such as euphoria are common. In some patients mild depression may occur. More serious manifestations such as confusion, frank psychosis and convulsions have been recorded.

6. Latent tuberculous focus may flare up.

7. There is always a danger of infections developing in a most insidious manner, temperature may be normal, E.S.R. may not rise, discomfort may be slight, and a dangerous condition may pass unnoticed.

8. Perforation of peptic ulcer without classical signs and symptoms may occur.

9. Osteoporosis may occur in post-menopausal women and bedridden patients.

10. Thrombosis is more likely to occur in persons under cortisone therapy.

Clinical indications for the use of corticosteroids and corticotrophin have been classified by Hench as follows:

*Group I:* Specific replacement therapy. Primary adrenal insufficiency, adrenal apoplexy, hypopituitarism, postoperative adrenal insufficiency, after adrenalectomy, adrenogenital syndrome, spontaneous hypoglycaemia.

*Group II:* Treatment of choice. Haemolytic anaemia, bronchial asthma, particularly status asthmaticus, dermatitis medicamentosa, acute inflammatory bursitis, lupus erythematosus, pemphigus vulgaris, early periarteritis nodosa, temporal arteritis, acute rheumatic polyarteritis and carditis, non-tropical sprue, acute non-suppurative thyroiditis.

*Group III:* Satisfactory treatment. Progressive rheumatoid arthritis, nephrosis, allergic dermatitis, severe delirium tremens.

*Group IV:* Therapy of limited value. Severe insect and snake bites, leukaemia, pruritus ani and vulvae, acute viral hepatitis.

*Preparations Available:* Cortisone acetate is available in tablet form for oral use; for intramuscular injections it is available as a fine crystalline suspension in aqueous medium containing a little benzoic acid. It is slowly absorbed from the site of injection and is not suitable when quick action is desired.

For urgent use intravenous preparations of cortisone hemisuccinate or cortisone and hydrocortisone as the free alcohol in ethyl alcohol solution are available. These preparations are usually given in 500 ml of normal saline as a drip. The intravenous route is preferred in acute adrenal crisis.

Hydrocortisone acetate is available in tablet form for oral use. Hydrocortisone is the only preparation useful when local effects are desired, as in joints, in the eye, or as topical skin applications.

*Modified Steroids:* Fried (1956) stated that the anti-inflammatory and anti-allergic properties of cortisone and hydrocortisone depend upon: (a) a-3-keto, 4, 5, unsaturated structure in ring A, (b) an oxygen atom in position 11, and (c) dihydroxy acetone chain at position 17. Retaining these three essentials, modifications in the molecular structure were made and the preparations studied; it was shown that introduction of a double bond between carbon 1 and 2 produced a marked increase in the therapeutic index without any change in the compound's salt retaining and potassium losing action (so called mineralo-corticoid action). Thus delta-1-dehydro-cortisone (prednisone) and delta-1-dehydro-hydrocortisone (prednisolone) were born.

Extensive clinical trials have been carried out with these modified steroids, prednisone and prednisolone. Both are three to four times more potent as antirheumatic and anti-inflammatory agents; as there is no proportionate increase in frequency or severity of undesirable side effects, these steroids possess a higher therapeutic ratio.

Prednisone and prednisolone can be considered having exactly the same action as cortisone and hydrocortisone, but with less mineralo-corticoid activity, weight for weight salt retention

## Hydatidiform Mole and Chorionepithelioma

is the same in all these compounds but the delta compounds being given in smaller doses are less likely to produce these effects.

With a safe dosage of 15 mg a day of prednisone or prednisolone, electrolyte and nitrogen imbalance are rare, hence in incipient or actual cardiac failure, the delta compounds are preferred. These compounds have been used with some success for their diuretic effect in heart failure, cirrhosis of the liver and with great promise in nephrosis. The mechanism involved in diuresis is partly due to increased glomerular filtration and partly due to competition of the corticoids with endogenous aldosterone for sites of sodium reabsorption in the renal tubules.

In all conditions where cortisone and hydrocortisone are used essentially for their anti-rheumatic or anti-inflammatory effect, these compounds can be given.

As replacement therapy in adrenal insufficiency states, because of their low mineralo-corticoid activity prednisone and prednisolone are not preferred to cortisone or hydrocortisone. Another compound, fluoro-hydrocortisone, has been shown to possess 10 times the antirheumatic effect of hydrocortisone, thus correspondingly smaller dose will be required to produce therapeutic effect, but it has been found to cause undue salt and fluid retention. It has no advantage over hydrocortisone for direct intra-articular therapy. It is possible that this compound will prove useful for maintenance therapy of patients with Addison's disease. Most patients could be maintained with 1 to 2 mg of fluoro-hydrocortisone with supplement of 1 to 2.5 mg of cortisone. Apart from this, it will be restricted to topical use.

**Dosage schedule:** Depending on the clinical results the total daily dose will vary for each individual patient. In children the dose will depend more on the condition to be treated than on age or weight of the child. In most cases the following schedule will be found suitable for cortisone.

Cortisone: 1st day—total 300 mg, divided in 3 or 4 doses.  
2nd day—total 200 mg divided in 3 or 4 doses.  
3rd day onwards, 100 g.

When favourable clinical results are noticed, the daily dose is gradually reduced to a minimum dose that will control the manifestations of the malady. This will vary with the individual patient and may be from 25 to 75 mg a day. The duration of treatment will vary according to the nature of the malady under treatment, from few days to few weeks. The final or temporary discontinuation has to be very carefully thought of, and should never be abrupt, but should be gradually tailed off.

**Hydrocortisone:** It is effective in smaller doses. The initial dose being from 80 to 100 mg a day divided into 4 doses till appreciable clinical improvement occurs, the maintenance dose will vary between 5 to 10 mg or even lower.

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## HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA

Probodh Das

Both hydatidiform mole and chorionepithelioma have received particular attention in recent years largely due to contributions by Novak and Seah<sup>1</sup>, Acosta-Sison<sup>2</sup>, Hertig and Mansell<sup>3</sup> and others<sup>4,5,6,7</sup>. Much newer knowledge has accumulated with reference to the incidence, pathology, clinical aspects and treatment of this condition.

**Hydatidiform Mole:** The incidence of hydatidiform mole in the Oriental countries is much higher than that in the Western countries. For example, the incidence in the Philippines is 1 in 146<sup>2</sup> and in India 1 in 447<sup>4</sup> as against 1 in 2,000<sup>3</sup> pregnancies in the U.S.A. This higher incidence in the Oriental countries is believed to be linked up with early pregnancy and higher parity<sup>4</sup>. Origin of cystic moles, according to Hertig and Mansell<sup>3</sup>, depends upon two factors: (i) Presence of functioning maternal circulation and (ii) absence of foetal circulation, a condition usually present between the 3rd and the 5th weeks of intrauterine life.

Chemical study of the fluids aspirated from living molar villi (McKay et al<sup>8</sup>) shows that it is of interstitial type, essentially similar in its composition to ascitic and oedema fluid. Moreover,

the fluid is retained within the molar villi against the force of a higher osmotic pressure exerted by the surrounding maternal serum. There is also relatively high concentration of amino acids within the molar fluid as compared to that of maternal serum.

Hypertension in cases of molar pregnancy, in the opinion of Acosta-Sison<sup>10</sup>, results from high titre of chorionic gonadotrophin and increased intra-abdominal pressure of the enlarged uterus, producing uterine ischaemia. He also noticed a difference in the order of appearance of the signs and symptoms of toxæmia. In normal pregnancy oedema appears first followed by hypertension, whereas in molar pregnancy the first manifestation of toxæmia is hypertension followed by albuminuria and oedema. Das<sup>4</sup> found the size of the uterus to be bigger than the period of gestation in 62.9 per cent, of the same size in 31.8 per cent, and definitely smaller than the period of pregnancy in 5 per cent. Both Acosta-Sison and Shears<sup>11</sup> give particular importance to the use of uterine sound in the diagnosis of hydatidiform mole. According to them, in the absence of passage of mole cyst, when the uterus is bigger than the period of pregnancy, there is no foetus, and the size of the uterus is more than 20 weeks' pregnancy, the ability to introduce gently the uterine sound unobstructed into the uterine cavity up to 9 or more cm is diagnostic of hydatidiform mole.

The importance of quantitative assay of serum chorionic gonadotrophin in the diagnosis of hydatidiform mole is stressed by Delfs<sup>12</sup>. In his opinion, gonadotrophin assay is not of value in making differential pathologic diagnosis between three types of cases, namely (i) hydatidiform mole, (ii) follow-up after mole, (iii) chorionepithelioma, but is of utmost value in separating seriously abnormal cases from uncomplicated ones during the follow-up period. The study shows that either a rising titre or a persistent gonadotrophin level above 20,000 I. U./litre, more than 30 days after evacuation of a mole is an indication of trouble.

Vaginal smear and hormonal determinations were made by Hsu, Lin, Ma and Lai (China)<sup>13</sup>. Both gonadotrophin and oestrogens varied in amount and 17-ketosteroids were low in all cases. They could not find any correlation between the amount of hormone production and prognosis. When vaginal smear shows discrepancies between gonadotrophin titre and acidophilic cells and lack of navicular cells, such a finding is suggestive of either hydatidiform mole or choriocarcinoma. If, along with this, there is low 17-ketosteroids excretion, the diagnosis is suggestive.

A review of recent literature shows lack of uniformity in the method of treatment of a case of mole<sup>14</sup>. Novak and Seah<sup>5</sup> suggest evacuation of the mole vaginally with ovum forceps. This is followed 4-5 days later by a careful curettage of the uterine cavity when the danger of uterine perforation will be much less.

**Chorionepithelioma** : Chorionepithelioma, in the opinion of Centaro and Mangione<sup>20</sup> can be considered as an endocrine neoplasm histologically derived from ovular chorion which presents all the characteristics of the glands of internal secretion. By analogy it can be compared to active tumours of the ovary, pituitary, adrenal and thyroid glands. The authors conclude that there is direct relationship in chorionepithelioma between the peculiar cellular structure which typifies those abnormal cells and varying degrees of functional activity observed.

The incidence of chorionepithelioma, like hydatidiform mole, is also higher in the Oriental countries than in the West. Hau and Pang<sup>15</sup> found the incidence as 1 per 114 autopsies or 1 in 3708 pregnancies. The study is based on 28 autopsied cases of chorionepithelioma in 3200 autopsies performed at the University of Hong Kong. The mean age of the patient was 30 years, the youngest being 19 and oldest 47 years. Largest number of cases occurred between the ages 26-35 years. There was no evidence of any relation between parity and chorionepithelioma. Primary growth was present in uterus in 19 cases and varied greatly in extent. When the primary growth was small or lacking, there was no parametrial infiltration and the distant metastases were extensive. But when the primary growth was extensive and accompanied by parametrial infiltration, the distant metastases were less massive. In the opinion of these authors both local and systemic resistance may develop towards chorionepithelioma. Evidence of this is found in the disappearance of the primary growth from the uterus and in the inverse relationship between parametrial infiltration and distant metastases.

The incidence of various types of pregnancy preceding the disease varies within wide limits as could be seen from the following figures. Hau and Pang<sup>15</sup> found molar pregnancy in 25 per cent, abortion in 29 per cent, full term pregnancy in 46 per cent. Hasegawa<sup>16</sup> in Japan on the other hand found, mole in 67.9 per cent, abortion in 25.4 per cent and full term pregnancy



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only in 6.3 per cent. The same author found that chorionepithelioma has higher incidence in induced or curetted abortion where dilatation and curettage was done 2-4 times than in spontaneous abortion. Acosta-Sison<sup>2</sup> found in 27 cases of chorionepithelioma, the preceding pregnancy as follows: hydatidiform mole in 62.96 per cent, abortion in 18.5 per cent, full term labour in 3.7 per cent and chorionepithelioma *ab initio* in 14.8 per cent.

Recent data from the Philippines<sup>16</sup> would seem to point out that undernutrition, rather than any racial factor is the underlying cause of chorionic malignancy. The average survival in Hau and Pang's series was 6 months, the shortest being 1 month, the longest 24 months. The period between the occurrence of chorionepithelioma and the last pregnancy is variable. The longest period reported is 17 years and occurred in a patient aged 59 years<sup>17</sup>.

The most common cause of death appears to be haemorrhage<sup>15</sup> from the tumour in various sites, the order of frequency being cerebral, vaginal, gastro-intestinal and abdominal.

Acosta-Sison<sup>16</sup> lays much stress on the early diagnosis and early institution of treatment. She thinks that chorionepithelioma is amenable to surgical treatment in at least 50 per cent of cases, provided the patients are operated on, early before metastases have occurred or metastases are still confined to the vagina or the lungs. Ogawa et al<sup>18</sup> found testosterone of value when used in conjunction with total hysterectomy and enucleation of metastatic lesion. Testosterone, 1000-2000 mg, is given within 1 month after operation and is followed by 100-200 mg per month. Four patients were treated thus with good results.

For inoperable chorionepithelioma Monaco et al<sup>19</sup> suggest intra-arterial chemotherapy. Li and his associates<sup>21</sup> report definite clinical improvement in three cases with methotrexate, a folic acid antagonist.

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## HYPERTENSION, TREATMENT OF

Rustom Jal Vakil

Recent excavations prove how very distant and far-reaching are the roots of our civilization. Man's interest in the heart and circulation probably began 30,000 years ago, with the Cro-magnon race, long since extinct. There are frequent references to the heart and arterial pulsations in ancient Egyptian, Indian and Chinese writings.

A serious study of high blood pressure was not however possible until 1893, when von Basch of Vienna, introduced the sphygmomanometer into routine clinical practice. Since that time, our knowledge of high blood pressure has grown by leaps and bounds. In spite of the massive literature that exists today, on the subject of hypertension, there is little unanimity of opinion about its causation, treatment or nomenclature.

Since high blood pressure or hypertension is a symptom or symptom-complex rather than a disease entity, and since the causative factor or factors are unknown in the great majority of cases, its treatment is necessarily disappointing. According to Fishberg, "the treatment of

essential hypertension is one of the many unsatisfactory chapters in therapeutics". In 1939, William Evans, after a trial of 33 widely acclaimed medicinal preparations in cases of high blood pressure, found them all valueless as anti-hypertensive agents. In spite of the apparent helplessness of the situation, as recent studies show, much can be done with newer hypotensive remedies to alleviate the suffering and disability of the hypertensive as well as to ward off or delay the onset of complications.

It is a mistake to regard hypertension, except perhaps in the case of a small minority of cases, as a compensatory or teleological phenomenon as was once believed by such great authorities as Janeway, Allbutt and Oliver. In view of the serious consequences of untreated high blood pressure, such a negative or *laissez-faire* attitude towards hypertension cannot but be deprecated.

Within the past few years, so many new preparations with blood pressure-reducing properties have been discovered, revived, synthesized and effectively tried out in the treatment of hypertensive states, that a knowledge of their pharmacological actions, and clinical uses proves indispensable to every single practising physician. Amongst the most noteworthy of these preparations may be mentioned *rauwolfia* and its alkaloids, veratrum and its alkaloids, ganglion-blocking agents, hydralazine, dehydrogenated ergot alkaloids, thiocyanates and chlorothiazide.

There is no standard line of treatment applicable to all cases of hypertension. Each case has to be judged individually on its own merits, the treatment required being to some extent dependent on the degree or grade of hypertension, the type of hypertension and on the individual preference of the clinician in charge.

**Rauwolfia Preparations.**—The plant *rauwolfia* (*rauvolfia*), named after the German physician and traveller Leonhard Rauwolf, is a twining herb or shrub belonging to the natural order Apocynaceae. Of the 130 odd species of *Rauwolfia*, about eight grow in India; of these species the most widely used and important is *R. serpentina*, which grows in the Himalayas, and in Deccan, Assam and Bihar. It has been used extensively in India for over 600 years, under its sanskrit designation of *serpagandha* (also variously known as *chandrika*, *chhota-chand*, *chand*, *dhanbarua*, *pagla-ka-dawa*, *harkai*, *karavi* and *atalagandhi*), for a host of unrelated ailments including dysenteries, diarrhoea, insomnia, insanity, fevers, insect stings and scorpion bites.

The *rauwolfia* plant has been mentioned in ancient Hindu manuscripts as far back as 1,000 and even 2,000 B.C. (Trease and Evans, 1954); it has also been described in the monumental writings of Charaka (second century, A.D.).

Until the year 1949, in spite of several notable contributions by Indian authors on the pharmacological and clinical properties of *rauwolfia* (Siddiqui and Siddiqui, 1931; Sen and Bose, 1931; Roy, 1931; Chopra and associates, 1933; 1941, 1942; Vakil, 1940; Paranjpe, 1942; Bhatia and Kapur, 1944; Gupta, Kahali and Dutt, 1944), interest in the drug remained confined to India. In 1949, with the publication of a clinical study on *rauwolfia* by the author for the first time outside India, interest in the subject of *rauwolfia* therapy of hypertension became worldwide within a matter of two years, as proved by a recent review of the subject (Vakil, 1955).

**Chemical Composition:** Numerous alkaloids of therapeutic value have been isolated from the root of the *serpentina* plant. In 1931, Siddiqui and Siddiqui were able to describe five alkaloids, viz. ajmaline, ajmalinine, ajmalicine, serpentine and serpentinine, the first three being classed as the ajmaline group and the latter two as the serpentine group. Since that time many more alkaloids have been isolated, one of the last and best known being *reserpine*, a complex heterocyclic compound related to yohimbine, isolated by Muller and associates in 1952. Other alkaloids, some of proved therapeutic value, have also been isolated since then viz., hypotensive (Chowdhury and Ghosh, 1953), sarpagine (Stoll and Hofmann, 1953), raupine (Bodendorf and Eder, 1953), rauhimbine and iso-rauhibine (Hofmann, 1954), substances I and II (Popelak et al, 1953) and reserpinine (Schlittler et al, 1954).

**Pharmacological Effects:** The pharmacological actions of *reserpine*, particularly on the central nervous and cardiovascular systems, have been subjected to intense scrutiny both at the bedside and in the experimental laboratory.

The tranquillizing effect of the alkaloid appears to be directed subcortically, mainly in the region of the hypothalamus. There is a decrease in central sympathetic activity, probably

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secondary to inhibition of afferent impulses to the pressor centers. Certain clinical side-effects of rauwolfia therapy, viz. tranquillization, hypotension, nose block, miosis, bradycardia and increased gastro-intestinal activity, are attributed to a relative preponderance of the para-sympathetic system (Kline and Saunders, 1957). The lowering of blood pressure after reserpine may also be due, but to a much smaller extent, to action of the alkaloid on other nerve centers in the brain-stem and on peripheral vessels. Ganglion blockade and adrenolytic effects have not been convincingly proved to be concerned in the hypotensive response (Kline and Saunders, 1957).

**Absorption and Fate:** The alkaloids of rauwolfia are well absorbed from the gastro-intestinal tract. In view of the long latent period and slow action, it is possible that the drug is converted into some other *active form* within the body, its final fate being unknown. The hypotensive response takes about 2 to 6 days to appear and disappears slowly in 1 to 5 weeks (Vakil, 1954-55). Fifty to 60 per cent of the oral dose is excreted by the kidneys within 3 to 4 hours of administration.

**Indications :** Rauwolfia exhibits a very wide range of applicability, being suitable for virtually every case of hypertension (renal, endocrine or secondary), irrespective of age, sex and other considerations. Although ideally suited for mild and labile cases of hypertension, it proves useful, when used in conjunction with other more potent anti-hypertensive drugs, even in severe, fixed and malignant forms of the disease.

Of late, rauwolfia has been used with great success in psychiatry, particularly for cases of mental excitement, anxiety and insanity.

**Contra-indications :** Although there are no definite contra-indications to the use of rauwolfia, it is best avoided in cases of diarrhoea or dysentery (in view of its stimulant effect on the intestinal musculature), during acute cardiovascular and cerebrovascular emergencies (such as coronary and cerebral thrombosis), in acute congestive cardiac failure, in the rare case of hypersensitivity or allergy to the drug (R.S. "hyper-reaction"), in cases of gastric or duodenal ulcer (because of increase of acidity in the stomach) and in certain types of mental depression and defectiveness (Kline and Saunders, 1957).

**Preparations :** For many years the only preparation of rauwolfia available was the crude root, either in powder or tablet form (*Serpina* tablets). Innumerable preparations of rauwolfia are now on the market and offer a choice of either the whole root or total alkaloids, the alseroxylon fraction, or one or other of the isolated alkaloids.

**Administration and Dosage:** Being orally effective, relatively non-toxic and inexpensive, rauwolfia preparations which require no laboratory control or supervision for administration, are ideally suited for non-hospitalized ambulant hypertensives.

There being no fixed schedule of dosage, the optimal dose of rauwolfia or its alkaloid has to be determined for each case. However, in about two-thirds of cases of essential benign hypertension, an average dose of crude extract, equivalent to 4 mg of total alkaloids or of 0.25 mg of reserpine, given thrice daily, brings about a satisfactory lowering of both systolic and diastolic pressures. In about a half of the cases which prove refractory to such doses, larger or massive doses produce satisfactory results. In a small percentage of cases, even minute doses—(e.g. 2 mg of total alkaloids or 0.2 mg of reserpine) bring about brisk falls in blood pressure. Whereas smaller doses usually suffice in the climacteric, psychogenic and labile forms of hypertension, even massive doses tend to fail in the malignant and renal forms of hypertension. In the latter, doses four or five times the average therapeutic dose may prove incapable of altering blood pressure levels.

**Clinical Results:** A hypotensive response, systolic and diastolic, is observed in more than two-thirds of hypertensives treated with *R. serpentina*.

In cases of uncomplicated benign essential hypertension, systolic and diastolic pressures are lowered in 70-80 per cent of cases after a month's treatment, either with the crude extract of *R. serpentina* or with the isolated alkaloid reserpine.

About 1 case in 5 of hypertension proves completely refractory to *R. serpentina* (the so-called "non-reactor").

Although, in most cases, rauwolfia lowers the systolic and diastolic pressures gently and gradually, 1 case in 5 responds to it with a sudden or sharp drop of pressure (the so-called "hyper-reactor") ; such a response may be either immediate or delayed.

The hypotensive response in the average case, takes about 2 to 6 days to appear, disappears slowly in 1 to 5 weeks, is independent of age, better in females than males, and is best marked in the labile form of hypertension.

The *persistence, consistency and predictability* of action of rauwolfia preparations have been demonstrated conclusively (Vakil, 1954).

The hypotensive action of *R. serpentina* tends to persist for 2 to 4 weeks after cessation of therapy. In benign essential hypertension the hypotensive effect was demonstrable 2 weeks after withdrawal, in about 80 per cent of cases. A hypotensive response was demonstrable over and over again in the same patient, on repeatedly resuming of treatment after withdrawal (Vakil 1949, 1953). The hypotensive and clinical response to rauwolfia preparations usually follow a constant pattern in a given individual, their nature and extent being often predictable before the resumption of therapy.

*Withdrawal symptoms* rarely develop even when rauwolfia treatment is interrupted suddenly or discontinued. *Habit formation* is not a feature of rauwolfia therapy; *craving* for the drug is not displayed even when it is withdrawn after long periods of administration.

Comparative studies on crude extracts and individual alkaloids of rauwolfia have not substantiated the alleged superiority of one form of preparation over the other. The results obtained by the author with different preparations of rauwolfia, from the points of view of clinical response, hypotensive action and side-effects, have been more or less similar.

*Subjective improvement* is noted by most hypertensives on rauwolfia. Apart from amelioration of hypertensive symptoms proper, e.g., headache, vertigo, tinnitus, precordial pain, and palpitation, a characteristic sense of tranquillity or well-being is induced. This is particularly true in climacteric, psychogenic and labile forms of hypertension. Clinical results are frequently disappointing in cases of malignant, nephritic and arteriosclerotic hypertension. *Objective findings*, such as the results of kidney and of liver-function tests, the electrocardiogram, teleradiogram and fundoscopic changes usually remain unaffected under treatment.

*Side-effects and Complications*: These are infrequent, mild and varied and may take the form of nose-block, lassitude, drowsiness, diarrhoea, slow heart action, vomiting, vertigo, increase of body weight, nightmares, nervousness, headache, fatigue, excessive salivation, dry mouth, oedema, anorexia or an increase of appetite. In rare cases, severe urticaria, bronchial spasm, circulatory collapse, mental depression, extrapyramidal signs, impotence or dermatitis have appeared after such therapy. As far as can be ascertained, not a single death has so far been reported from the use of rauwolfia alone (Vakil, 1954 and 1955; Kline and Saunders, 1957). The accidental ingestion of ten times the usual therapeutic dose has caused no more than a mild and temporary upset in one of the author's cases.

In view of the wide margin of safety between therapeutic and toxic levels of the drug, even large doses are well tolerated; this is particularly so in cases of psychoses.

*Summary and Conclusions*: Advantages of rauwolfia therapy are many and varied. It is universally applicable (being useful in virtually every case of hypertension), easy to administer, requiring no special care or facilities and is orally effective, its action being consistent and predictable. Its action tends to persist for 2 to 4 weeks after cessation of therapy. Serious side-effects, common to other hypotensive agents, are rarely encountered. Withdrawal symptoms, acquired tolerance, craving and habit formation do not occur. Subjective improvement with rauwolfia is often remarkable; apart from an amelioration of the hypertensive symptoms, a characteristic sense of tranquillity or well-being is induced. Besides, the drug shows remarkable additive or synergistic properties when used in conjunction with other hypertensive agents.

In spite of its wide range of usefulness, it must be noted that rauwolfia is not a powerful hypotensive agent, is of little value during hypertensive crises or episodes, frequently induces nasal stuffiness or obstruction which may be severe enough to make the patient abandon therapy, and is not sufficient medication for the severe malignant and renal forms of hypertension.

Rauwolfia preparations, on the basis of an extensive and worldwide experience, have now come to be rightly regarded as mild, non-toxic, widely applicable and inexpensive hypotensive agents of proved value.

**Veratrum Preparations.**—The veratrum plant, of which the best known species are *Veratrum viride* (U.S.A.) *Veratrum album* (Europe) and *Veratrum subadilla* (Mexico and West Indies), is a liliaceous plant belonging to the suborder Melanthaceae. The roots and rhizomes of *Veratrum viride* and *album* and the seeds of *Veratrum subadilla* are the sources of the veratrum alkaloids.

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**Chemical Composition:** There are over a dozen alkaloids in *Veratrum viride* alone. Three main groups of alkaloids are distinguishable, viz., *amine* alkaloids or alkamines, *ester* alkaloids and *glycosidic* alkaloids. Most preparations depend on the presence of the therapeutically potent *ester* alkaloids, protoveratrine A and B. The complex chemistry of these alkaloids has been fully reviewed by Jacobs and associates (1945).

**Pharmacological Actions:** The *hypotensive* action of veratrum is due to peripheral vasodilatation of neurogenic origin, which in turn is due to : (1) The Bezold reflex (Bezold and Hirt, 1867), the afferent fibres being vagal and arising from the left ventricle, lungs, carotid sinus, carotid body and nodose ganglion, the efferent pathways being not as yet clear. The Bezold effect is comprised of a reflex fall of blood pressure with a slowing of the heart rate. (2) A "central" effect, through inhibition or chemoreceptor buffers. In normal subjects and in hypertensives, the following cardiovascular effects are observed after veratrum therapy, viz., (1) a fall of systolic and diastolic pressures, and (2) a decreased total peripheral resistance with increase of peripheral blood flow. In therapeutic doses, the alkaloids do not exert any deleterious action on *renal* function; the cerebrovascular resistance is decreased, but the cerebral blood flow remains unaltered (Moyer et al, 1953 ; McCall, 1953). *Ganglionic* and *adrenergic* blocking effects are not observed.

**Absorption and Fate:** The alkaloids of veratrum are absorbed from the gastro-intestinal tract as well as from subcutaneous and intramuscular tissues, the rate of absorption being 5 to 20 times greater with the intramuscular than with the oral route. The fate of the alkaloids within the body is not clear. A small fraction is excreted by the kidney.

**Preparations :** Two main forms of veratrum preparations are available, viz. (1) partially purified alkaloidal mixtures or extracts made from *veratrum viride*, e.g., Veriloid (Riker), Vergitryl (Squibb), Vertavis, Veratrone and Alkavervir, and (2) purified alkaloids e.g. protoveratrine A and B (Veralba) made from *Veratrum album*.

**Indications :** Veratrum preparations are useful in cases of hypertension, essential or malignant, toxæmias of pregnancy, and in certain cases of renal disease, particularly pyelonephritis or glomerulonephritis.

**Contra-indications** to veratrum therapy are coarctation of aorta, phaeochromocytoma, digitalis poisoning, quinidine therapy, raised intracranial tension, chronic uræmia, cerebrovascular disease, angina pectoris and coronary thrombosis.

**Administration and Dosage:** *Veriloid* (Riker), an alkaloidal mixture, *biologically* standardized in dogs, is available in tablets of 1 and 2 mg for oral administration. The hypotensive action of the drug is *variable*, and depends on the rate of absorption from the gastro-intestinal tract and on its rate of excretion ; the optimal dose of the drug is that which gives a satisfactory hypotensive response without nausea ; it varies from case to case. In most cases, the range between the "nausea threshold" and the level for an optimal hypotensive effect is wide enough to permit a satisfactory stabilization of dosage.

The initial daily dose of Veriloid is from 9 to 15 mg given in 3 doses at 6 to 8 hour intervals, the evening dose being 1 to 2 mg larger than the morning and afternoon doses. The initial dose of Veriloid recommended is 9 mg for small patients and for mild or moderate hypertension, and 12 to 15 mg for severe hypertension and for overweight cases.

The amount administered daily is then increased by 1 mg increments or less to each of the daily doses every third or fourth day, until the maximum dose without nausea is determined. Early signs of intolerance to the drug are oesophageal or substernal burning with or without sialorrhoea.

"Long term" treatment is usually safe, acquired tolerance to the drug being rare. A slight reduction in dosage is indicated in case of increased *reactivity* to the drug. The maintenance dose may be continued, with minor adjustments for long periods of time. In some, it is possible to reduce the dose even after months of treatment.

**Side-effects :** Drawbacks to veratrum therapy are the narrow margin of safety between therapeutic and toxic doses and the constant supervision and attention to dosage required.

Usual side-effects are substernal or epigastric burning, excessive salivation, bad taste, nausea, vomiting, hiccup and sweating. Less common but more serious symptoms are tingling or numbness of fingers or lips, hot sensations, heat over the head, neck or shoulders, blurring of vision,

mental symptoms, pulse irregularities, hypotension, syncope, circulatory collapse, bronchial spasm, and depression of respiration.

**Advantages :** Theoretically, veratrum is ideal because it causes widespread dilatation of the vessels of the brain and kidneys, does not interfere with normal vasomotor lability or reflexes, does not cause postural hypotension and its effects are often dramatic in acute hypertensive episodes and in malignant hypertension. Excellent results in essential hypertension have been reported with the drug, by Hite (1946), Freis (1949), and Wilkins (1949).

**Disadvantages :** The margin of safety between the therapeutic and toxic doses is narrow ; toxic symptoms, especially nausea and vomiting, are common. Results are seldom spectacular with oral medication. It has no place in the treatment of mild or asymptomatic cases. The course of the disease is not materially altered by therapy. Unsatisfactory results have been reported by McNair, 1948 ; Coe et al, 1950 ; Mills and Moyer, 1952 ; and by Gropper et al, 1951.

**Ganglion-Blocking Agents.**—Within the last decade, innumerable new synthetic agents have been elaborated with a view to “block” or neutralize the nicotinic effects of acetyl choline. Amongst these so-called ganglion-blocking agents or ganglionic paralyzants, capable of blocking autonomic ganglionic and neuro-muscular transmission, one of the most useful series of compounds elaborated independently by two groups of workers (Barlow and Ing, 1948 ; Paton and Zaimis, 1949) is the “polymethylene bis-trimethyl ammonium” series, commonly referred to as the *methonium* series. The most useful members of this series are the hexamethonium (C6), pentamethonium (C5) and decamethonium (C10) compounds.

**Pharmacological Actions :** Most of the pharmacological effects of the ganglion-blockers are attributable to a blocking effect or inhibition of synaptic transmission of nerve impulses from the pre-ganglionic to the post-ganglionic neurones in the autonomic ganglia. This is due to a selective action of the drug on the post-synaptic membrane, raising the threshold of the ganglion cell to acetyl choline liberated by the pre-ganglionic neural discharge.

The ganglion-blocking drugs lower the arterial blood pressure (hypotensive response), raise the heart rate, enhance peripheral blood flow, increase renal plasma flow and lower renal vascular resistance. The hypotensive effect is usually marked but variable in hypertensives and minimal or poor in normotensives ; postural hypotension which is prominent, especially in the upright posture, is reduced by adopting the recumbent posture or by resort to muscular activity.

**Hexamethonium.**—Hexamethonium, or C6 of the methonium series, has been widely employed as the chloride, bromide or bi-tartrate salt (under the trade names of “Methium”, “Esomid” and “Bistrium”) particularly in cases of hypertension but also for peripheral vascular diseases, hypertensive heart disease, pregnancy toxæmia, duodenal ulcer and pink disease.

Hexamethonium is usually preferred to pentamethonium for high blood pressure cases because of its greater effectiveness and lesser tendency to cause nausea or tachycardia. In the treatment of hypertension with hexamethonium, parenteral medication is far more predictable and potent (ten to twenty-five times as potent) than oral therapy ; the hypotensive response may be greatly enhanced by a salt-free diet ; protracted therapy in malignant hypertension may cause fatal renal breakdown, uraemia and death.

In hypertensive cases, hexamethonium may be employed (1) for the routine treatment of cases of moderate to great severity, (2) for hypertensive crises or complications (e.g. encephalopathy, pulmonary congestion and eye complications), (3) for the amelioration of refractory symptoms (e.g., headache and vertigo, etc.) and (4) for selecting cases suitable for dorso-lumbar sympathectomy.

**Administration and Dosage :** Hospitalization is desirable but not mandatory during hexamethonium therapy. Constant observation and care are necessary, particularly during the initial phases.

The initial *oral* dose of the drug is usually 125 mg given three times a day (with meals or on an empty stomach before meals) to ensure uniform absorption and maximal results. It is better to start with small doses (e.g. 125 mg once or twice daily) in cases on a low-salt diet, in post-sympathectomy cases and in cases of hypertensive encephalopathy, such cases being over-susceptible to the action of the drug. In ambulatory cases, it is better to increase the dose at intervals of 4 to 7 days ; in hospitalized cases, daily increments are permissible. The optimum dose varies from case to case and even in the same case from time to time. Although some

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tolerate as much as 5 g of the drug daily, it is better not to exceed a daily dose of 3 g. Withdrawal of medication should be gradual unless serious reactions necessitate sudden interruption of therapy.

Hexamethonium may be administered intravenously (with saline or dextrose solution) or preferably subcutaneously. The initial dose need not exceed 1.25 to 5 mg. A gradual increase is then effected over several days until the optimal depressor dose is established (usually between 20 and 100 mg). The subcutaneous injection is usually repeated at intervals of 8 to 12 hours. As tolerance develops, the dose has to be increased to several times the initial dose; within a few weeks however, the effective level becomes stabilized, requiring no further increment.

*Side-effects* : Reactions to therapy may be mild or severe. Amongst the *milder side-effects* are dry mouth, visual disturbances, difficulty of accommodation, mydriasis, conjunctival suffusion, hesitant micturition, chilliness, constipation, anorexia, heart-burn, nausea, eructations, bitter taste, abdominal discomfort, postural giddiness and syncopal attacks. Amongst the severe reactions are sudden hypotensive spells, paralytic ileus, constipation, urinary retention, anginal pain, syncope, collapse, pulmonary dyspnoea, uraemia and death.

*Therapeutic Results* : Whilst Moyer et al (1953), recorded success in 81 per cent of cases of hypertension, others have not been so enthusiastic about results.

In my experience, a satisfactory response has been obtainable in over one-half of cases of moderate or severe hypertension ; in such cases, normal or almost normal blood pressure levels have been attained and maintained, amelioration of hypertensive symptoms (e.g. headache, tinnitus, retinopathy and cardiac failure) noted and some of the previously incapacitated hypertensives resorted to normal healthy occupations.

**Pentolinium Tartrate**.—Marketed under the trade name of Ansolysen (M & B), pentolinium tartrate or pentamethylene - 1 : 5 - bis (1 - methylpyrrolidinium) hydrogen tartrate, is one of the latest and most useful of the ganglionic paralyzants.

*Preparations* : For oral use, it is available as 40 mg and 200 mg tablets, and for subcutaneous injection as an aqueous solution (5 mg or 25 mg per c.cm) and as "retard solution" (25 mg per c.cm).

*Indications* : The drug is of value in benign essential hypertension, severe or malignant hypertension, arteriosclerotic hypertension, hypertension with renal complications and in peripheral vascular diseases.

It is best avoided in cases of recent coronary or cerebral thrombosis and in organic pyloric stenosis.

*Administration and Dosage* : The drug may be used either orally or subcutaneously depending on the patient's response to test doses, on the severity of the disease and on whether it is used for initial therapy or maintenance treatment.

*For effective medication*, preliminary "test doses" must be employed in gradually increasing fashion, the degree and duration of blood pressure response being noted; individualization of dosage is essential.

The initial oral dose need not exceed 10 or 20 mg; with 10 mg increments on successive days, the dose may be gradually stepped up to the effective oral dose (usually between 20 to 100 mg, two to four times daily). Tablets are dissolved in water and administered half an hour before meals. With increasing tolerance developing, doses may be gradually stepped up to required levels.

When administered subcutaneously, the initial dose should not exceed 25 mg. With increments of 0.5 to 1 mg the dose is gradually stepped up to the effective hypotensive dose (usually 2.5 to 10 mg). This is repeated on subsequent days with smaller supplementary doses at 6 or 8 hourly intervals. For maintenance treatment, the "retard" solution may be substituted for the 'aqueous' solution.

*Side-effects* : Dryness of the mouth, disturbance of accommodation, sweating, nausea, heartburn, gastro-intestinal stasis, difficult micturition, transient impotence, dilated pupils, conjunctivitis, dizziness, yawning, fainting or postural giddiness may be noted during therapy.

*Advantages* : Pentolinium presents several advantages over hexamethonium. An oral response is obtainable in a larger percentage of cases ; small doses prove effective in maintaining effective hypotensive levels ; its action is more prolonged, whilst drug tolerance is much less marked.

It has been widely employed (both singly and in combination) with success, in cases of hypertension by Smirk (1952) and others.

**Mecamylamine Hydrochloride.**—Marketed under the trade name of Mevasine or Inversine (Sharpe & Dohme & Merck), mecamylamine hydrochloride or 3-methylaminoisocamphane hydrochloride, is a new synthetic ganglionic blocking agent which has gained considerable popularity within a very short period.

**Advantages :** Because of its almost complete absorption when administered orally, greater predictability of action, greater potency, more gradual onset of effect, longer duration of action and smoother blood pressure response, mecamylamine is preferred by many to hexamethonium for cases of high blood pressure.

**Administration and Dosage:** Usually supplied as 10 mg compressed tablets for oral administration, therapy is commenced with 2.5 mg mecamylamine twice daily (morning and evening), preferably after meals. The initial dose is then increased by increments of 2.5 mg at intervals of two days or more until an optimal hypotensive response is obtained.

The total daily dose required ranges from 5 to 120 mg, with an average of 20 or 25 mg. It is usually administered in two to four divided doses. Both initial and maintenance doses are usually regulated by blood pressure readings taken in the standing or erect posture.

By combining mecamylamine therapy with rauwolfia or reserpine, it is possible to potentiate the hypotensive action whilst reducing unpleasant side-effects.

**Indications and Contra-indications:** Mecamylamine is ideally suited for moderately severe, severe and malignant cases of hypertension. It is best avoided or used with caution in cases of recent myocardial infarction, coronary sclerosis or insufficiency, cerebral arteriosclerosis, renal insufficiency and pyloric stenosis.

**Side-effects :** As with other ganglionic blocking agents, anorexia, nausea, vomiting, constipation, fatigue, orthostatic hypotension, syncope, dry mouth, dilated pupils, urinary retention or ileus may arise during mecamylamine therapy.

**Clinical Results:** A significant hypotensive response has been claimed in over 90 per cent of cases of moderately severe to severe hypertension. The drug is said to ward off the malignant phase of hypertension and bring about considerable amelioration in the symptoms and signs of the disease.

**Hydralazine.**—Hydralazine (hydrallazine) or 1-hydrazinophthalazine, marketed under the trade name of Apresoline (Ciba) is a moderately potent hypotensive remedy with a wide applicability. It has come into prominence lately as the result of Reubi's observation that it increases renal blood flow, an observation confirmed clinically by Schroeder (1952) and Page and McCubbin (1941).

**Pharmacological Actions:** Hydralazine causes a moderate reduction of systolic and diastolic blood pressures, augments renal and splanchnic blood flow, causes a significant relaxation of cerebral vascular tone and promotes coronary vasodilatation in isolated hearts.

The hypotensive action is due to combination of a central effect probably in the region of the mid-brain, a mild degree of adrenergic blocking effect and an inhibitory influence on endogenous pressor substances, such as angiotonin or hypertension. Amongst anti-hypertensive remedies, hydralazine is unique in augmenting renal blood flow.

**Absorption and Fate:** Hydralazine is well absorbed both from the gastro-intestinal tract and the tissue depots. In view of its delayed effect, it is said to be converted after absorption into some active metabolite. About 4 to 6 per cent of the dose administered is recoverable in the urine.

**Preparations :** For oral use, hydralazine is available as 10, 25 and 50 mg tablets. For parenteral use, it is available in 1 c.cm ampoules containing 20 mg of the active substance.

**Indications :** Hydralazine is of value in essential benign hypertension, pregnancy hypertension, post-sympathectomy hypertension, and acute diffuse glomerulonephritis.

**Contra-indications :** It is best avoided or used with caution in coronary heart disease, cerebrovascular disease, severe renal damage, later stages of malignant hypertension, chronic glomerulonephritis and in conjunction with barbiturates or alcohol.

**Administration and Dosage:** In ambulatory cases, the parenteral route of administration is best avoided. In a case of hypertension of moderate severity, a 10 mg dose is administered



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orally, 4 times a day (after breakfast, lunch, dinner and at bed time) for 2 to 4 days. Mild symptoms of headache, palpitation, giddiness, anxiety, and postural vertigo are common but disappear spontaneously within a week or two. The dose is then gradually stepped up by 25 mg increments at intervals of 6 to 8 days until a dose of 75 to 100 mg four times a day is attained. The optimal daily dose for maintenance purposes varies from case to case, but is usually somewhere between 100 mg and 600 mg per day.

In the event of *tolerance* to the drug, it is best to discontinue it for a week or ten days, after which a re-start of treatment yields a far more satisfactory response.

In *hospitalized* cases, *treatment* may be speeded up considerably either by larger initial doses and rapid increments or by resort to parenteral administration.

*Side-effects* : The incidence of side-effects can be reduced by resort to small initial doses, slow increments in dose and by a *judicious forewarning* of the patient about side-effects. Common side-effects are headache, palpitation, rapid heart rate, dizziness, weakness, nausea, vomiting and postural hypotension. Less common are constipation, nasal congestion, lachrymation, conjunctivitis, urticaria, skin rash, drug fever, localized oedema (periorbital, genital or dependent), flushing, numbness and tingling of the extremities or lips and anaemia.

Occasionally observed are difficulty in micturition, gastro-intestinal haemorrhage, pancytopenia, "low-salt" syndrome, acute rheumatoid state, disseminated lupus, acute psychotic episodes, anxiety state, severe depression, coma, dyspnoea and anginal symptoms.

*Therapeutic Results*: Excellent results have been claimed with the drug by Schroeder (1952), Hafkenschiel and Lindaner (1951), Johnson, Freis and Schaper (1952) and Page (1951). According to Goodman and Gilman (1955), it reduces the blood pressure significantly in 50 per cent or less of unselected cases of hypertension.

In Vakil's experience hydralazine is particularly useful for cases of moderate or severe essential hypertension (grades II and III) and for some cases of malignant or grade IV hypertension. When used in conjunction with rauwolfia, smaller or *sub-toxic* doses may suffice in bringing down the pressure to safer levels ; it is particularly useful for cases of diastolic or diastolic-systolic hypertension (where the diastolic element of the hypertension is preponderant or proving refractory to therapeutic measures) and for cases of hypertension showing impairment of renal function.

When employed in conjunction with rauwolfia, even severe cases of hypertension may be controlled with total daily doses of hydralazine not exceeding 75 or 100 mg. By this method, severe reactions can be eliminated and milder reactions rendered less annoying to the patient.

**Hydrogenated Ergot Alkaloids.**—Dihydroergocornine, dihydroergocristine and dihydroergokryptine were prepared by Stoll and Hofmann, in 1946, by hydrogenation of the corresponding ergot alkaloids ergocornine, ergocristine and ergokryptine. Rothlin and associates (1946) showed that the hydrogenated compounds, unlike the parent compounds, cause dilatation of peripheral vessels, thus lowering both normal and elevated blood pressures.

Hydergine (Sandoz) contains the three hydrogenated alkaloids, dihydroergocornine, dihydroergocristine and dihydroergokryptine, in equal proportions.

*Pharmacological actions* : The hypotensive action of Hydergine has been attributed to a central depression of postural cardiovascular reflexes, a central stimulation of the vagal nuclei (Nickerson, 1951), and a central inhibition of sympathetic impulses (Bluntschli and Goetz, 1947).

*Preparations* : The hydrogenated ergot alkaloids are marketed as sublingual tablets (0.25 mg Hydergine per tablet) for oral use and ampoules (0.3 mg Hydergine per c.cm) for intramuscular and intravenous use.

*Indications* : Hydergine has been recommended for essential hypertension, toxæmias of pregnancy, phaeochromocytoma, peripheral vascular disorders, coronary insufficiency and angina pectoris.

*Dosage and Administration*: The "injection test" is used to assess the individual's response to the drug. 1 or 2 c. cm of the drug are injected intramuscularly after 30 minutes of rest in the recumbent posture. A depressor response of over 20 mm systolic or 10 mm diastolic pressure, lasting for over half an hour, as is common in cases of labile hypertension or of essential hypertension (grades I and II), suggests suitability of the case for Hydergine treatment.

In labile or mild cases of hypertension, with good response to the "injection test", oral treatment usually starts with 1 tablet on the first day, 2 on the second and so on, until 7 tablets are administered on the seventh day; after this, a maintenance dose of 1 to 8 tablets daily is established.

*Combined Oral and Parenteral Therapy* is indicated in severe cases and cases refractory to oral medication. In such cases, besides oral treatment 1 to 2 c. cm (0.3 to 0.6 mg) of the drug are injected intramuscularly or subcutaneously, daily or every other day, a series of 10 to 40 injections constituting a course of treatment. Treatment may be continued intermittently for 3 to 4 months, after which an attempt is made to gradually bring down the dose.

*Side-effects*: Nausea, vomiting, weakness, or nasal stuffiness may be observed during treatment.

*Results*: Contradictory results have been reported in hypertension on Hydergine therapy. Whilst satisfactory lowering of blood pressure and subjective improvement were reported in essential hypertension by Goetz (1950), Josephs (1940) and Gibbs (1952), little or no benefit was observed by Dupuy (1952) and by Stutton et al (1952).

**Thiocyanates.**—Sodium and potassium salts of thiocyanate (sulfocyanate or rhodanate), marketed as tablets, capsules and elixirs for oral administration, have been employed on and off since 1900, for the treatment of high blood pressure cases.

Because of serious toxic reactions, thiocyanate therapy had been abandoned, until 1936, when Barker re-emphasized its utility and suggested regulation of dosage on the basis of periodic determinations of the serum thiocyanate level. Since that time, thousands of hypertensives have been treated with this form of therapy.

*Pharmacological Actions*: These are not clear in spite of years of experience with this mode of therapy. The *hypotensive action*, reported in from 40 to 70 per cent of cases, has been variously attributed to (1) a central sedative action, (2) a direct spasmolytic nitrite-like effect on peripheral blood vessels, (3) decreased cardiac output, (4) a slow reduction of serum sodium with sodium depletion, (5) an action on endocrine glands (particularly thyroid and adrenal cortex), (6) a mild histotoxic hypoxia or protoplasmic poisoning due to liberation of the poisonous cyanide ion from thiocyanate and (7) to an effect on cholesterol metabolism.

According to Corcoran et al (1945), thiocyanates improve *renal function*, the glomerular efferent arteriolar resistance being decreased or unchanged and tubular secretory activity increased or unchanged.

Amongst its other actions may be enumerated a goitrogenic action with symptoms and signs of hypothyroidism, a disturbance of calcium metabolism with tendency to osteoporosis, and iodide-like effects on the skin and mucous membranes.

Sodium and potassium thiocyanate are freely absorbed from the intestinal tract, being distributed mainly within the extracellular fluid depots.

*Dosage and Administration*: There is no fixed dosage for thiocyanate therapy, since renal excretion and blood levels vary widely from case to case.

An essential requisite for safety in treatment, as stressed by Barker (1936), is a periodical checking-up of the serum thiocyanate levels. During initial phases of treatment, the serum level is maintained between 6 and 12 mg per 100 c. cm (Barker, 1936) or between 3 and 6 mg (Corcoran, 1945). According to Barker, mild toxic symptoms are usually noted with levels of over 15 mg and fatalities may occur with levels over 40 to 50 mg per cent. During the first 2 months, the level is determined once weekly. After the maintenance dose is determined, the serum levels are kept between 4 and 6 mg, serum determinations being carried out once or twice monthly.

The initial dose should not exceed 100 mg 3 times a day (daily dose of 300 mg). In case of poor response, the dose may be increased very gradually after 3 weeks, but not exceeding a total daily dose of 750 mg. The average maintenance dose is 200 to 400 mg per day.

*Toxic Effects*: Toxic manifestations are many, varied and frequent, the margin of safety between therapeutic and toxic doses is narrow or non-existent.

Mild reactions such as fatigue, weakness, lassitude, malaise and drowsiness are encountered in practically all cases. Less common are anorexia, epigastric pain or discomfort, nausea,

## Hypertension, Treatment of

vomiting, diarrhoea, headache, giddiness and skin eruptions. Much less common but far more serious are exfoliative dermatitis, insomnia, confusion, dysarthria, motor aphasia, ataxia, hallucinations, delirium, mania, convulsive fits, psychosis, peripheral neuritis, osteoporosis with arthralgia, goitre with hypothyroidism, frank myxoedema, dyspnoea, chest pain, palpitation, thrombophlebitis, anaemia, nephrosis, falling hair, corneal ulcers, decrease in libido, cachexia, and hepatic necrosis.

**Clinical Results:** Thiocyanate therapy has unquestionably a salutary effect on hypertensive symptoms like dizziness, insomnia, palpitation and particularly headache; although it lowers blood pressure in the majority of cases, it does not prolong life or alter the course of the disease; it requires constant care, supervision, co-operation of the patient and laboratory facilities; toxic symptoms are both frequent and hazardous; it has no effect on malignant hypertension.

**Chlorothiazide.**—A non-mercurial oral diuretic, marketed under the trade name of Diuril (Merck, Sharp and Dohme), chemically known as 6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide, has been recently employed with success by Hollander and Wilkins (1957) in the treatment of arterial hypertension.

**Administration and Results:** With an oral dose of 250 mg three times a day (and with a normal dietary salt intake), a hypotensive response of from 20/10 to 60/30 mm Hg, was noted, within 1 to 3 weeks of treatment, in 9 of 17 hypertensive subjects (Hollander and Wilkins, 1957).

Chlorothiazide appears to be a useful diuretic and hypotensive agent for cases of arterial hypertension, complicated or uncomplicated by congestive heart failure.

**Pharmacological Actions:** Besides being a powerful diuretic, chlorothiazide displays an anti-hypertensive action in cases of raised blood pressure. Recent studies suggest that the depressor action of the drug is due to some hitherto undetermined direct hypotensive action rather than to alteration in body fluids or electrolytes.

**Side-effects:** Apart from transient weakness and fatiguability in about twenty per cent of cases, nausea in ten per cent, and cramps, flushing and paraesthesiae in a few, the drug appears to be remarkably free of toxic side effects (Wilkins).

**Summary and Conclusions.**—(1) There is no standard line of treatment or specific remedy applicable to all cases of hypertension; individualization in treatment is essential. (2) Innumerable hypotensive remedies of proved value have been made available to the practising physician within the past two decades. A working knowledge of their pharmacological actions, indications, contra-indications, dosage, modes of administration and side-effects, is essential before these remedies can be suitably applied to clinical practice. (3) The rauwolfia preparations (including the whole root and individual alkaloids) are the most useful, economical, least toxic and the most widely applicable of all the known hypotensive agents. Ideally suited for mild cases rauwolfia or its alkaloids can be suitably combined with more potent depressor or hypotensive agents for the treatment of moderately severe or severe cases of hypertension. With combined therapy (collateral therapy), the synergistic or potentiating effect of rauwolfia on other pressure-lowering drugs can be utilized to advantage. (4) For moderately severe or severe cases of hypertension, resort may be had to the ganglionic blocking agents or to hydralazine, chlorothiazide or veratrum alkaloids, preferably in conjunction with rauwolfia preparations. (5) In the event of renal involvement, hydralazine appears to be the drug of choice, it may be used either singly or in conjunction with rauwolfia. (6) In the event of a cardiovascular or cerebrovascular emergency or of congestive cardiac failure, complicating a case of hypertension, ganglionic paralyzants being strongly contra-indicated, resort may be had to one or other of the milder hypotensive remedies.

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**HYPERCALCAEMIA, IDIOPATHIC**

*J. B. Mehta*

Idiopathic hypercalcaemia produces a clinical picture of an infant 3-4 months old who does not gain weight, vomits, and is constipated. Deposits of calcium in the kidney and elsewhere (calcinosis), bony changes of osteosclerosis including cystic appearances, hypercalcaemia, hypercalciuria, hypertension, azotaemia and decreased alkaline phosphatase in blood occur. A benign and a more severe forms are described<sup>4</sup>. The picture resembles hypervitaminosis. In a survey by the British Paediatric Society 204 cases were found in the United Kingdom over a period of 1½ years<sup>1</sup>. Morgan et al found a 4.6 per cent incidence of admissions to the hospital<sup>6</sup>. No case seems to have been described in India. Few reports have appeared from Germany, Greece, Finland, Sweden, but none from the U.S.A. and Canada, which is strange since the feeding habits of these countries and Britain are similar<sup>2,4</sup>. It has been shown that fortified milk and milk powders in the U.S.A. contain appreciably less vitamin D (National Dried Milk, U. K., contains 1400 I.U./quart and dried milk in the U.S.A. 487 I.U./quart)<sup>2</sup>.

Is there a relationship to vitamin D? The British Paediatric Society reported that proprietary infant foods contain a very appreciable amount of vitamin D and the habit of giving extra vitamins may produce a state of excessive vitamin D intake. Yet they were not convinced that vitamin D as such was the cause of the idiopathic hypercalcaemia. It has been suggested that these cases are hypersensitive to vitamin D. However, there seems more grounds for considering it a separate entity<sup>2</sup>. There is increased absorption of calcium and phosphorus and it is not influenced by vitamin D addition to diet. Urinary phosphatase is increased in hypervitaminosis D but decreased in idiopathic hypercalcaemia. Another interesting finding is a raised blood cholesterol. Cholestaemia is a state found in other renal diseases, suggesting that the primary defect is in the kidney. Vitamin D is also a steroid derivative<sup>3</sup>. Relation to parathyroid is also suggested—immaturity of the renal tubules to respond to parathyroid hormone and to cause excessive calcium reabsorption from the tubules<sup>5</sup>.

Vitamin D definitely aggravates the condition. A diet low in calcium and vitamin D is difficult to prepare for infants, as it means excluding milk and its products. However, low-calcium milk powder (Locasol, Trufood) and low calcium cereal foods (Farola, Glaxo) are available. This dieting is enough in the less severe cases. Cortisone and ACTH help in reducing serum calcium levels. EDTA (Disodium ethylenediamine tetra-acetic acid) is effective but produces gastric irritation<sup>6</sup>. Alkalis should be avoided. Diets with high phytic contents, like those containing cereals, help in preventing calcium absorption from the intestine.

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**HYPERTROPHIC GASTRITIS—See GASTRITIS**

**HYPOFIBRINOGENEMIA IN OBSTETRICS**

*K. Bhasker Rao*

*Hypofibrinogenemia in Obstetrics*<sup>1,2,3</sup> is seen in (1) accidental haemorrhage, (2) amniotic embolism (3) missed abortion with retention of dead foetus, (4) vulval haematoma, and (5) dextran transfusion. It may result from depletion of fibrinogen in circulation by its precipitation as fibrin by thromboplastic material from the placenta or liquor amnii; or by the destruction of fibrinogen by fibrinolysins produced by tissue injury. As a result, bleeding tendency is developed. It was first noticed by De Lee, in 1901, in cases of accidental haemorrhage and its cause was correctly identified by Dieckmann, in 1936. Haemorrhagic symptoms appear when the fibrinogen level falls below 100 mg per cent. After a spontaneous delivery in a severe accidental haemorrhage, the uterus may contract but there may still be uncontrollable bleeding. In concealed accidental haemorrhage when this coagulation defect is present, it has to be corrected before surgery is undertaken. The longer the delay in delivery in these cases, the worse the condition becomes, though within 48 hours after delivery the fibrinogen level spontaneously

## Hypotensive Anaesthesia in Surgery

returns to normal. In intrauterine death of the foetus, this condition is noticed only after the 4th month of gestation provided the conceptus is retained over 5 weeks after the apparent foetal death. This condition can be detected by Schneider's test for clotting. Treatment consists in giving a litre of fresh blood or 4 g of human fibrinogen intravenously and repeated if necessary. Double strength dried plasma is also useful.

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## HYPOPHYSECTOMY FOR CANCER—See PITUITARY GLAND

## HYPOPITUITARISM—See PITUITARY GLAND

## HYPOPLASTIC ANAEMIA OF CHILDHOOD—See ANAEMIA, HYPOPLASTIC, OF CHILDHOOD

## HYPOTENSIVE ANAESTHESIA IN SURGERY

R. J. Maneksha

In major surgery 50 per cent of the surgeon's time and a great deal of his nervous energy are devoted to controlling bleeding. The rest is concerned with the real object of operation. MacIndoe presents his experience with hypotensive anaesthesia in over 4,500 cases operated at the Queen Victoria Hospital, East Grinstead, during a period of 4 years.

The systolic pressure is maintained at 60 mm Hg at heart level by using a ganglion-blocking drug, pentolinium tartrate (Ansolsen). The resting tissues of the human body are adequately supplied with blood at this pressure provided there is vasodilatation and full oxygenation. The site of operation is elevated above the heart level. A slow return of blood pressure post-operatively is necessary as this will prevent oozing. The patient is kept in a special recovery department and confined to bed in reversed Trendelenburg position (at about 150°). It is vitally important to maintain a clear airway.

The safety of the operation will depend upon the skill of the anaesthetist and the competence of the surgeon. All major head and neck surgery is ideally suited for this type of anaesthesia.

There were 5 fatalities in the early stages.

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## INFANT FEEDING

P. Tirumala Rao

**Introduction.**—The problem of infant feeding habits, and nutrition of preschool children (upto the age of 5 years) has assumed global importance. The prevention of the incidence of malnutrition and promotion of optimum growth patterns of children are necessary as a first step towards building up positive health of human race. Hence a study of the local traditional infant feeding habits of millions of children, who live in varying socio-economic, climatic, and cultural situations has become very important and urgent. A review of the nutritional problems in the Central American population and in countries like India revealed that generally the food habits of the lower economic groups all over the world appear to be similar<sup>4,9,12</sup>.

The first half of this century has seen outstanding contributions in these types of infant feeding habits, and the work during this period has placed infant nutrition on scientific basis. Advances in milk technology and recent discoveries of various growth-promoting factors, even without addition of substantial quantities of milk, which is not easily available to the bulk of the masses in the underdeveloped areas, hold out the hope of solving the infant feeding problems on a rational and at the same time, on a practical basis in the near future<sup>5</sup>.

**Some Recent Concepts :** (1) There are four recent developments that offer great potentialities for improving the health of people everywhere in the next decade<sup>6</sup>. They are :

- (a) The "empty calor" concept (an attempt to reduce carbohydrate and fats).
- (b) The amino acid fortification of basic cereal grains.
- (c) The growth-promoting effects of vitamin B<sub>12</sub>.

(d) Certain antibiotics like tetracycline and oxytetracycline given orally (especially in children who live in unhygienic surroundings).

(2) *Curd Tension*: Modified cow's milk has significantly replaced breast milk in infant feeding in many countries. The difficulties of digesting cow's milk in the infant stomach are due to the fact that it contains only 15 per cent lactalbumin and 85 per cent calcium caseinate (which forms large protein curds and is not digested easily) in contrast to human milk, which contains only 40 per cent calcium caseinate<sup>7</sup>.

Newer methods evolved on the basis of improved understanding of biochemistry since 1912, have led to the modification of the casein in cow's milk and reduction of the "curd tension" which obviates the difficulties of undiluted cow milk feeding of previous years.

Various scientific studies have shown that it is the "curd texture" and not the acidity that is of prime importance in the digestibility of milk in the infant stomach. No fundamental changes have been made since 1935 towards a change of this concept.

Curd tension is measured in grams. The ideal score of any milk is a curd tension of zero. Human and evaporated milks are examples of milk with zero curd tension. Many proprietary manufacturers claim zero curd tension of their products. Curd tension below 20 to 33 g is satisfactory for use.

**Recent Studies of Infant Feeding Habits in Tropics and Sub-Tropics.**—(a) *The Change in the Method of Weaning*<sup>4</sup>: The large scale milk dairying and advancement in milk technology made a change in the basic pattern of infant feeding from human milk—semisolid food, to human milk—cow's milk—semisolid food, at a very early age period.

It is of importance to realise that for economic, climatic and sometimes cultural reasons, the basic two-stage pattern of weaning from breast to semisolid food is still customary in many tropical countries.

(b) *The Concept of Child as Parasite of the Mother*: It has been presumed since a long time that the infant receives all its nutrition from the mother irrespective of her nutritional status. Congenital beri beri, early nutritional deficiency syndromes and congenital defects produced experimentally, established the prime importance of adequate maternal nutrition, especially in the first and last trimesters of pregnancy.

Low birth weight of a child is the first manifestation of maternal malnutrition in majority of the studies.

(c) *Prolonged Lactation in Lower Economic Groups*: At first site though one is tempted to criticize this habit as a cause of malnutrition amongst infants in the tropics, it must be realised that this is the only source of biologically important protein these mothers could afford to give their children during the first two years of life<sup>4,12</sup>.

Gyorgy described the presence in human milk of a growth factor, a special strain of "Lactobacillus bifidus" (L. bifidus, var. Penn). The presence of this factor might explain why human milk can adequately nourish infants despite its low protein content. Moreover, human milk, presumably, is superior to cow's milk in encouraging a characteristic pattern of the intestinal bacterial flora<sup>2</sup>. Though breast milk of the ill-nourished mother is lacking in many essential vitamins and minerals and other growth factors which produce specific deficiencies when the child is kept on breast for prolonged periods, the ill-nourished mother is able to maintain the protein content of her breast milk, by a process of adaptation<sup>4</sup>.

(d) *Some Problems of the Artificially-fed*: Even in many advanced countries, studies of artificially fed children revealed that they were receiving inadequate calories and over dosage of vitamins, specially vitamin D, for want of proper instructions to mothers<sup>3, 6</sup>.

A good rule to provide adequate milk mixture is one level packed measure to each ounce and one standard teaspoonful of sugar to every four ounces of milk mixture. Half the infant's weight in pounds is the volume in ounces of a four hourly feed and the number of level measures. On such mixtures, children have been able to stand well high caloric feeding (120 calories/kg body weight)<sup>3, 6</sup>. Some children who were receiving only tinned milk feeds in infancy, developed convulsions due to a deficiency of vitamin B<sub>6</sub>; they were relieved by administration of B<sub>6</sub>. Stored milk foods should therefore be used cautiously.

In India buffalo milk is freely available and can be used for infant feeding after removing the excess fat by skimming or after dilution of the milk. There is little difference in the essential amino acid content of buffalo and cow's milk<sup>10</sup>.



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(e) *Importance of Vegetable Proteins*: Many studies in India and in Central America have shown that when vegetable proteins are selected properly, they help to substitute animal proteins and prevent the incidence of malnutrition. Studies in the early period of breast feeding revealed that the generally accepted figure of protein requirements in early infancy, of 3.5 g/kg of body weight is probably an over-estimate and the actual requirement may not be more than 2 g/kg in the first few weeks, probably less in the later stages. This gives some hope of solving the protein problem in infant feeding<sup>11</sup>.

(f) *Certain Peculiar "Negative Habits" which Affect Infant Nutrition*: (1) The habit of giving castor oil or other purgatives too frequently, during the major part of infancy (this has been observed both in the Indian and the Central American Studies).

(2) Coffee or tea as milk substitutes to young infants.

(3) Giving only carbohydrate diets in post-weaning period.

(4) Lack of balanced vegetable or animal proteins in the weaning foods.

(5) Traditional prejudices due to customs, religious or otherwise, and lack of education concerning certain available nutritious foods.

Education about these "negative habits" further improve the nutritional status of these children who are already lacking in proteins in their diet<sup>12</sup>.

*Basic Nutritional Requirements*<sup>7, 4</sup>: (1) *Proteins*: 2 to 2½ oz. of breast milk and 1½ oz. of cow's milk per pound of body weight provide 1½ to 2 g of protein per pound of body weight. Excess of protein is well tolerated.

(2) *Carbohydrates and Fats*: Adequate for the calories. Excess of fat is not well tolerated by children. One-third of the carbohydrate should be derived from the milk and the remainder is obtained in the form of supplemental carbohydrate foods and sugars.

(3) *Minerals*: All the minerals like calcium, phosphorus, etc. are taken care of when adequate milk is given. The following are the requirements per day—calcium 1 g, phosphorus 1.5 g, iron 10 mg, iodine trace.

*Iron*: Both in artificially fed and breast-fed infants, iron deficiency occurs by about six months unless iron-containing foods like egg yolk, cereals, vegetables and fruits are added by this time. This is specially true of those children who are mainly fed on cow's milk. The iron deficient mother, the supplemental diet like rice which has low iron content, the poor absorption due to various factors including chronic gastro-enteritis, changes in the intestinal epithelium in mal-nutritional states such as Kwashiorkor and the presence of severe ascariasis or any infection known to produce a transient hypochlorhydria, generally contribute to the iron deficiency anaemia in tropical infants.

Normally the foetus receives 300 to 500 mg of iron from the mother during its intrauterine life. The foetal stores could be further improved by taking care of the umbilical cord at the time of birth. By tying the cord after the cessation of pulsation or after quickly milking it down towards the foetus, about 100 c. cm of maternal blood is added to the infant, which provides about 45 mg of iron, which is more than what the infant retains in the entire first six months of its extra-uterine life.

(4) *Vitamins*: Vitamins A, D and B<sub>12</sub>, necessary for optimum growth are provided when a child gets about 24 oz of human milk or 18 oz of cow's milk per day. Both cow's milk and human milk are deficient in vitamins C and D. The minimum requirement of vitamin C is 30 to 50 mg per day and 400 I.U. of vitamin D. Excess of vitamin D should be avoided. Infants receiving 2000 I.U. of vitamin D per day did not develop better than infants receiving 135 I.U. and far less than those given 400 I.U. Both these vitamins are recommended to be given during early infancy. Excess of all vitamins is to be avoided.

In the tropics, scurvy is found to be infrequent amongst breast-fed infants due to some unknown reason. When we advise early administration of supplementary articles of diet like fruit juice to the infants in lower economic groups, we should be cautious, as there is the danger of inducing a fatal gastro-enteritis in them, who are otherwise growing well on the breast. This is due to the unhygienic surroundings and poor hygienic habits of these masses. But this should not deter us from instituting proper feeding habits after adequate education.

In the tropics, though there is no need for extra vitamin D, majority of the children are not exposed properly to the ultraviolet rays of the sun in early infancy on account of living in low-

roofed huts and crowded localities and being covered with clothes even when carried outside. Though rickets is not as common as other nutritional deficiencies, the need to expose the infants to sunlight should be borne in mind.

**Recommended Methods of Infant Feeding in the Tropics and the Sub-Tropics<sup>2</sup>.**—(1) *Feed the mother during pregnancy* with locally available nutritious foods, to give birth to a child with good weight, and good foetal storage of vitamins and minerals.

(2) *Feed the mother during the period of prolonged lactation* with adequate calories and proteins (including plant protein combinations).

(3) *Breast feeding could be prolonged for 1½ to 2 years*, depending on the situation in the lower socio-economic groups, either in the tropics or elsewhere. A good diet to the mother with adequate protein ensures better feeding of the child. In the mother the conversion of carotene to vitamin A is carried out better than in the child.

(4) *Introduce semi-solid food at the age of six months.* Cereals like rice, maize, wheat, ripe banana, etc. Later, within a short period introduce a diet containing egg yolk, vegetables, etc.

In preschool children (1 to 5 years.) where milk is not freely available or afforded, a preparation with the following recipe should be given :

Roasted Bengal flour	..	4 parts
Skimmed milk powder	..	1 part
Jaggery	..	0.5 part can be given with benefit.

On an average one ball weighing 33 g provides 7.5 g of protein and 120 calories<sup>8</sup>. Free use of skimmed milk could prevent and cure Kwashiorkor without the need of any further dietary supplements<sup>1</sup>.

(5) *Avoid certain "negative habits"* like giving castor oil, and other purgatives, and supplements like coffee, tea, etc. The idea of adequate food producing adequate bowel movement is to be promoted<sup>12</sup>.

(6) *Feeding in post-diarrhoeic periods*: The usual habit of prolonged feeding on cereal waters during this period (rice kanji, arrowroot kanji and other gruels) result in nutritional oedema. Hence modified skimmed milks, butter-milk, apple powder (apolona), banana feeds, carob bean powders with high content of legnin and pectin acting as absorbing and detoxicating agents (aroban) could be given, to build up the gradual food tolerance of the child, in the initial period.

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#### INFANT HEALTH

A. K. Niyogi

Prematurity has been stamped as the main cause of infant mortality and as such it has received lot of importance in the present day investigations carried out in the different parts of the world.

Miller and Snaith<sup>1</sup> in Newcastle (England) consider prematurity as the main cause of still birth. Half of the still births and more than half of neonatal deaths, in the cases investigated, were found in prematurely born babies. Douglas and Mckinlay<sup>2</sup> studied 94,716 births in Scotland and found that among the prematurely born, still births were 17 times and neonatal

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deaths 25 times more common than in full term ones. With regard to the "length of pregnancy" they found that, the chance of survival was better with longer pregnancy period as, all born before 30 weeks of pregnancy were either still born or died within the first month, two-thirds of those born within 30-34 weeks of pregnancy, one-third of those born within 34-38 weeks of pregnancy and one-fifth of those born after 38 weeks, had similar fate.

Drillien and Richmond<sup>3</sup> analysed 7157 births in Edinburgh between October 1953 and October 1954 and came to the conclusion that prematurity rate increased by double, with mothers' age beyond 20 and 34 years on either side. As regards maternal age, Bound, Butler and Specter<sup>4</sup> also found that in those more than 30 years, some increase in perinatal deaths and in those more than 35 years' age, a sharp rise in perinatal deaths occur both in primiparae and multiparae. The former workers had observed that prematurity rate rises after second births. In social classes III, IV and V taken together, it is 18 per cent for the sixth and subsequent pregnancies. Drillien and Richmond<sup>3</sup> in the above investigation also found that the low rate of prematurity and big babies are more common in those with prosperous economic background and that, the prematurity increases with illegitimate (premarital) births. In their cases, prematurity among illegitimate births was 13.3 per cent while that in legitimate births was 11.3 per cent.

Bound and his associates<sup>4</sup>, while surveying the causes of perinatal deaths, found by correlation with post-mortem findings that two thirds of perinatal mortality were caused by pulmonary syndrome, birth-trauma, pneumonias and intraventricular haemorrhage.

Follow-up surveys by several investigators show that the prematurely born children are at a disadvantage in later life (see "Child and Adolescent Health").

Sen<sup>5</sup> investigated 355 new born babies in West Bengal and Bihar and found a correlation between certain anthropological measurements (taken soon after birth and after four days) and the socio-economic status of the parents. For groups I and II, the measurements of the babies were higher than those in group V as are shown below :

	<i>Groups I and II</i>			<i>Group V</i>	
Crown to heel length (in inches)	..	..	..	19.103	18.480
Circumference of head ( " )	..	..	..	13.252	12.757
Biparietal diameter ( " )	..	..	..	3.655	3.489
Occipito-frontal length ( " )	..	..	..	4.470	4.318

Drillien and Richmond<sup>3</sup> had found that in social groups I and II 62.5 per cent babies had a birth weight over 7½ lb, whereas in groups IV and V babies over 7½ lb, it was 38.2 per cent. Surajnandan Prasad<sup>6</sup> in his survey of 865 cases born in the Hospital for Women, Patna, found that 450 boys had an average weight of 5 lb 15 oz, 347 girls had 5 lb 14 oz and 68 were born prematurely. First-born children had smaller birth weights, as in 224 first-born children the average birth weight was 4 lb 14 oz.

A study of neonatal blood pressure was undertaken by Holland and Young<sup>7</sup>. Systolic blood pressures at birth in normal infants were compared with those of others who were adversely affected. In 54 normal cases the mean pressure at birth was 69 mm Hg rising to 93 mm in six months. In 14 cases of foetal asphyxia, the mean pressure was 53 mm at birth, this reached normal level within six weeks. In 15 cases of premature infants, 54 mm pressure was found at birth, which reached normal figure within three months and in 36 cases of abnormal pregnancy with toxæmia, 62 mm was found at birth.

Miller and Snaith<sup>1</sup> suggested that for prevention of prematurity, attention to nutrition and treatment of anaemia and infection of the mother should be the watchword.

Since institutional care is more likely to prevent at least some of the perinatal deaths, it might be profitable to study the findings of Heady and Morris<sup>8</sup> who investigated 6,45,000 single births in England and Wales in 1950. They found that the percentage of institutional births declined with social class, as from 79 per cent in class I to 51 per cent in social class IV. They also found as regards parity, that more the parity, the less the institutional deliveries. They found that 78 per cent of first pregnancy, 57 per cent of the second, 33 per cent of the sixth to the tenth pregnancies and 40 per cent of the eleventh and later pregnancies attended institutions for under-going labour. It would appear thus that, the multiparous mothers of poorer classes should be particularly advised to undergo institutional delivery and antenatal advice, to reduce the number of perinatal deaths and premature births.

Verhoestraete<sup>9</sup> contrasted variations in the problem with respect to difference in technical development. In under-developed countries, he found that the loss of childbirth is high. Among three fifths of the world population, infant mortality exceeds 100 per 1000 live births. In this group excessive deaths in the first four years of life were also caused by preventable diseases such as gastro-intestinal, respiratory and parasitic infections. The influence of adequate nutrition is also important. The author suggests that since health services in these countries will develop slowly, specific programme like providing increased protein in diet, good water supply, proper breast feeding, etc., should be undertaken first, instead of an overall implementation of health programme. Millis<sup>10</sup> studying the influence of breast-feeding on weight gain in infants, did not find any disadvantage of artificial feeding after 24 weeks provided the weaning diet was adequate.

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## INSULIN COMA TREATMENT

N. S. Vahia

Insulin coma treatment is still very widely used in the treatment of schizophrenia. It is more useful in the cases of short duration. It gives good results in the first six months. Improvement rate with the insulin coma treatment in the cases of schizophrenia of more than two years' duration is so low that it is almost equal to the natural remission rate, and therefore this treatment is best given in cases of schizophrenia of less than six months' duration. Insulin coma treatment is not found to be very useful in juvenile schizophrenia. Amongst different types of schizophrenia the paranoid and catatonic types respond more satisfactorily than the simple and hebephrenic types.

Plain insulin is given intramuscularly on an empty stomach in the early morning. The patient is starved for 4-5 hours after which the effect of insulin is neutralized by giving food, particularly glucose. Increasing dosage of insulin produces more severe hypoglycaemic reaction till the patient goes into coma. This generally happens between 2 to 4 hours after the injection. The coma is maintained at the superficial or deep level, depending upon the therapist. As a rule deep coma is not maintained for a long period because of the risk of complications and mortality. The coma is terminated by feeding with the gastric tube or by intravenous glucose and the patient is kept well fed for the rest of the day. Details regarding the technique, various stages of coma and possible complications are given in any text-book on psychiatry and therefore have not been described in detail here. Two most important complications are prolonged coma and delayed coma.

Although this treatment is used very extensively in schizophrenia, there is considerable difference of opinion regarding its mode of action. After all, as long as the aetiology of schizophrenia is obscure, any treatment of this condition is bound to be empirical. Bourn<sup>4</sup> is very critical of the value of the insulin coma treatment. He believes that the evidence for the value of this treatment is not very convincing. According to him, it does not affect long term prognosis.

Lifschutz<sup>5</sup> studied 89 cases of insulin coma and compared the results with closely matched group of controls. Only short term results were studied. The insulin coma group had almost the same number of improved patients as control group. When electrical shock treatment was

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used it was at least as effective as insulin coma treatment. He concluded that this therapy had little value by itself.

Boling<sup>3</sup> and others compared the results of deep and light insulin coma treatment in 75 psychotic patients. The immediate clinical and psychological improvement and follow up studies in these cases showed no difference between the results of light and deep insulin coma.

Ackner et al<sup>1</sup> studied 50 schizophrenics aged between 18 to 40 years with a history of psychosis of 1 year duration, randomized separately according to the sex and diagnostic subtypes into insulin and barbiturate groups. The two groups were treated in the same ward under similar conditions. The only difference being that in one, coma was produced by insulin and in the other by barbiturates. At the end of six months after the treatment no significant difference was found in the two groups, suggesting that insulin coma treatment was not a specific therapeutic agent.

Whitehorn and Betz<sup>7</sup> reported on 109 schizophrenic patients who were treated by 18 physicians. The results were compared when insulin was combined with psychotherapy and when psychotherapy was used alone, in relation to the outcome of treatment. They suggested that active personal participation of the therapist during the insulin coma treatment was associated with good quantitative and qualitative improvement.

Boardman<sup>2</sup> suggested that chlorpromazine might be more effective treatment than insulin in previously untreated cases of schizophrenia.

A fourteen years' follow up of 780 patients, who received insulin coma therapy in schizophrenia, by West and his colleagues<sup>6</sup>, disclosed that this treatment produced immediate improvement or remission in 67.7 per cent in their patients. 63.3 per cent of those that had originally improved, relapsed—44 per cent within 1 month and 78 per cent within one year. And the second insulin course led to improvement in 52 per cent of 122 patients, who had relapsed. Electrical convulsive treatment was given with this treatment in many of these cases. They considered that insulin coma therapy had the immediate effect of restoring a schizophrenic patient to prepsychotic adjustment, but this was not accompanied by permanent resistance to schizophrenia. Long term intensive psychotherapy would be required to correct the underlying factors.

There is considerable criticism regarding the conclusions drawn by some of these workers and it is generally believed that the conclusions are not justified by the work presented by them but the important point is that some of the workers doubt the specific value of insulin in schizophrenia.

Insulin coma treatment is used extensively in Russia and the impression is that it probably helps in deepening inhibitory process and detoxication of unknown toxins in this condition. It is particularly considered to be useful in schizophrenia associated with delirium and hallucinations.

The overall impression thus, is that the insulin coma treatment in schizophrenia, is still a useful treatment, particularly for those cases that do not respond to tranquillizers, but the nature of action of this treatment is still a matter of opinion. One group of workers believes that it is the care and attention and the psychotherapy associated with it that is more important in this treatment. According to others, there is some relationship between insulin coma itself and the patient's improvement, because according to them psychotherapy by itself or by any other drug or group of drugs does not produce the amount of improvement that one sees with insulin coma treatment.

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## INTRACRANIAL COMPLICATIONS OF EAR DISEASES

J. V. DeSa

With the advent of antibiotics the picture of otogenic intracranial complications has changed remarkably. Though the mortality is stated to have fallen to 1/10th of the pre-antibiotic era, new problems such as resistance of organisms and masking of early symptoms continue to create unwarranted difficulties.

**Suppurative Meningitis:** This condition still occupies a prominent place in the lethal complications. Commonest organisms are pneumococci, streptococci or meningococci. Today the infection occurs, mostly, as a fulminating development in poorly nourished infants with otitis media. Despite antibiotic therapy the death rate is stated to be near about 30 per cent. Death may result, though gross evidence of meningitis has largely or completely disappeared. Bastrump-Madsen and Norby consider the ear to be so often a source of infection, that even in the absence of aural signs it is regarded as otogenic. A bilateral exploratory mastoidectomy is not unjustified in their opinion.

**Acute Encephalitis and Brain Abscess :** In the pre-antibiotic days brain abscess claimed a toll of nearly 50-100 per cent. Recent figures indicate that it still amounts to 25-30 per cent of all cases.

Courville states that the lesions today are almost invariably " adjacent lesions " of the temporal lobe rather than the cerebellum, the proportion being 2: 1. Anaerobic organisms are occasional invaders making the course of the malady rapid and resulting in a " diffuse brain abscess".

The treatment of otogenic brain abscess is still a controversial issue between methods of wide drainage with exploration and those of repeated aspiration and instillation of antibiotics and radioopaque material. No substantial references are available to support either of these methods in the last few years.

**Lateral Sinus Thrombosis:** The course of events in lateral sinus thrombosis has changed in the last few years, but the incidence is still high and almost the same as in pre-antibiotic days. The resistance of organisms has evolved a new problem in the management of the cases.

Two varieties of thrombi have been stated to occur frequently :

1. Septic thrombus or infection thrombus ;
2. Marantic or primary thrombus.

Marantic thrombus involves primarily the longitudinal sinus and develops from inanition and dehydration resulting in change in quality and quantity of blood. The mortality is high since the occlusion of venous channels leads to oedema, petechial haemorrhages and softening of basal ganglia.

The treatment has undergone modifications in the light of antibiotic and anticoagulant therapy. However, the eradication of the primary focus followed by thrombectomy is still the fundamental principle in treating a case. Ligation of internal jugular vein is advocated in cases of septic thrombus. Jugular ligation may also become necessary in case the patient fails to show clinical improvement, despite the preliminary thrombectomy.

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**INTRALOBAR BRONCHOPULMONARY SEQUESTRATION—See BRONCHOPULMONARY SEQUESTRATION, INTRALOBAR**

## IRON THERAPY

M. N. Guruswami

During the last decade studies of iron metabolism have elucidated the causation and therapy of iron deficiency anaemias. Our present knowledge indicates that (1) very little iron is excreted or lost from the normal body (less than 1 mg/day), (2) the body stores of iron are carefully conserved and there is reutilisation of the iron of breakdown haemoglobin and (3) iron equilibrium in the body is maintained by regulation of iron absorption (Hagedorn, 1956)<sup>10</sup>.

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Granick's work (1951)<sup>9</sup> has shown the specific function of intestinal mucosa in regulation of iron absorption. His observations on "mucosal block" and carriage of iron across the mucous membrane have helped the understanding of many problems concerning iron absorption. The amount of iron absorbed is regulated by the amount of ferritin (a complex ferric hydroxide phosphate aggregate plus the protein apoferritin) in the mucosal cells of the intestinal wall and this in turn is related to the need for iron in the body. When ferritin content of mucosa is low, more iron is absorbed and *vice versa*. Normally, very little iron is absorbed, even if given in large amounts, but in chronic deficiency large quantities are absorbed. It has been shown that in chronic anaemia there is increased absorption; probably hypoxia is a stimulant for iron absorption.

Laurell (1952)<sup>13</sup> reviewed the present trends of opinion regarding iron transport in the organism. In the plasma, iron is carried by the protein transferrin and iron leaves and enters the blood stream in ionised forms. The pH and redox levels in plasma and different cells are of great importance for the actual iron ion activity. During increased haemopoietic activity more than 10 per cent of the total amount of plasma iron passing through the bone marrow is retained, proving the rapid dissociation of iron-transferrin complex in the body. The equilibrium between iron ion activity in plasma and different organs is established rapidly. Variations of the serum iron during health and disease are probably due to several factors of which the variations of transferrin level, the amount of available storage iron (ferritin), the relative rate between the formation and destruction of the various iron containing porphyrin compounds and the iron demand of the reticuloendothelial system are the most important. The low serum iron level during infections and allied conditions may be due to iron being temporarily accumulated in the reticuloendothelial system in a form unavailable for intermediate iron metabolism.

Radioactive iron ( $\text{Fe}^{59}$ ) has many practical as well as experimental applications in the study of normal and abnormal metabolism of iron. It may be used to measure the absorption of iron from the intestines, to determine the rate of its clearance from plasma, and rate and amount of the incorporation into the red cells, to detect its organ localisation and movements within the body, and to quantitate urinary, menstrual or gastrointestinal loss of blood (Fabi et al, 1956)<sup>7</sup>.

In the adult male chronic iron deficiency invariably indicates blood loss or defective absorption of iron as in chronic diarrhoea, gastric resection, gastrojejunostomy or perhaps achlorhydria. In women, in addition to the above, chronic loss from menstruation, acute blood loss during parturition, foetal demands for iron during pregnancy and lactation may lead to a higher incidence of iron deficiency. In infancy and childhood, iron deficiency anaemia may result from haemorrhage, insufficient natal reserves, insufficient dietary intake, interference with absorption, or chronic infection.

Iron deficiency anaemia occurs in a fair proportion of pregnant women and may cause considerable maternal mortality. It can be either pre-existing anaemia aggravated by pregnancy or intrinsic anaemia induced by physiological demands of pregnancy exceeding dietary intake of haemopoietic materials.

<i>Authors</i>	<i>Percentage of cases treated</i>	<i>Percentage of haemoglobin</i>
1. Scott and Govan, 1949	20	Below 60
2. Lillie et al, 1954	23.5	„ 67
3. Doyle and McGrath, 1954	31.4	„ 80
4. Holly, 1955	54	Moderate deficiency
	26.3	Severe deficiency
5. Davidson, 1957	25	Below 80

Occurrence of anaemia in pregnancy.

From W. M. Davidson<sup>4</sup>, 1957.

It is recommended that haemoglobin level should be estimated at the first visit of every expectant mother at an antenatal clinic regardless of the period of gestation. Every expectant mother should routinely receive iron. The haemoglobin level should be estimated again

between the 32nd and the 36th weeks to determine whether it has been maintained and if not, there is still ample time for the restoration of haemoglobin level (Edgar and Rice, 1956<sup>5</sup>, Davidson 1957<sup>4</sup>).

During pregnancy, the mother has to provide 300-500 mg of iron or 1-2 mg a day for her baby (Cathie, 1957)<sup>3</sup>.

It is important to know whether the amount of elemental iron present in a preparation is the effective amount required. The following is a table condensed from Hagedorn (1956)<sup>10</sup>, illustrating the point :

<i>Iron salt</i>	<i>Iron content (per cent)</i>	<i>Mg iron in 300 mg salt</i>	<i>Amount needed in mg to furnish 25 mg of utilisable iron</i>
Ferrous sulphate	20	50	600
Ferrous sulphate, exsiccated	30	90	400
Ferrous sulphate, anhydrous	37	110	333
Ferrous gluconate	12	36	1000
Ferrous carbonate	16	48	800
Ferrous ammonium citrate	17	50	7000

Edgar and Rice (1956)<sup>5</sup> effectively treated routinely every expectant mother with iron as ferrous sulphate in 9 gr doses.

Davidson's (1957)<sup>4</sup> choice of oral iron is ferrous gluconate. Good response is observed with very little digestive disturbance. In difficult cases, ferrous succinate may be tried, but it is an expensive preparation.

Haler (1952)<sup>11</sup> prefers for children ferrous gluconate and ferrous succinate because they are better tolerated and have higher utilisation factors.

Oral administration of iron is not always possible and parenteral route may have to be resorted to on occasions. Hagedorn (1956)<sup>10</sup> considers the following as justifiable indications for parenteral therapy :

- (1) Intolerance or sensitivity to oral iron, e.g. chronic ulcerative colitis;
- (2) Unresponsiveness to oral iron even after adequate trial—idiopathic hypochromic anaemia explained probably due to some inherent defect in the mucosal ferritin barrier;
- (3) Cases in which maximal rate of haemoglobin regeneration is required as in severe iron deficiency in anaemia discovered late in pregnancy.

Parenteral iron preparations are at present extensively used clinically by an intravenous or an intramuscular route.

Since Nissim's first successful report on the use of *intravenous iron* in iron deficiency anaemia, extensive trial has been given to the compound saccharated iron oxide (Iviron, Astrafer, etc). Intravenously administered iron is retained almost quantitatively by the body. It should be given only to patients suffering from iron deficiency anaemia and in doses calculated to restore only the deficit of haemoglobin and the depleted stores of iron.

Hagedorn (1956)<sup>10</sup> recommends 25 mg of intravenous iron as the elemental iron, for every one per cent deficiency of haemoglobin content, assuming 100 per cent to be normal, in most cases of simple iron deficiency anaemia. In severe cases 200—500 mg of i.v. iron may be added. No case should get more than 2,000 mg of intravenous iron during one course. The schedule is 50 mg initially followed by 100 mg once or twice daily.

Davidson, (1957)<sup>4</sup> recommends the following intravenous technique. On the first day, a test dose of 1 ml should be given; if there is no reaction, 2.5 ml are given on the second day followed by 5 ml containing 100 mg of iron each day until the desired total dose is reached.

However, intravenous medication has a number of drawbacks. There may not be any visible or palpable veins suitable for giving intravenous injections, especially in children. The injection



## Iron Therapy

must be given by a medical practitioner and if not done carefully extravasation may occur leading to severe local pain, swelling and staining of the skin. Even with great care venous thrombosis with permanent occlusion is a frequent complication. Unpleasant allergic reactions, with a few deaths have been reported following intravenous iron therapy (Editor, B.M.J., 1954<sup>6</sup>, Hagedorn, 1956<sup>10</sup>, Librach, 1953<sup>14</sup>).

Nissim (1954)<sup>15</sup> states that toxic reactions may be mild or moderate, early or delayed. Early reactions occur within ten minutes, common even after small doses—probably allergic. Delayed reactions are infrequent, particularly occur with large doses, probably due to the slow precipitation of the compound when the material is injected rapidly or if pulmonary capillary bed is greatly reduced by disease.

Ross (1957)<sup>16</sup> treating 802 anaemic patients with intravenous saccharated iron oxide, observed a number of toxic reactions in 7.5 per cent cases given 100 mg doses and 43 per cent with 500 mg doses; 5 per cent in simple iron deficiency but 24 per cent when there were complications like fever, toxic or metabolic disturbances. He concludes that even with careful selection and the standard 100 mg dose, incidence of reaction will remain at about 5 per cent; hence the necessity for less toxic parenteral iron preparation. This has led to the preparation of less toxic and easily administered *intramuscular iron* (e.g. Imferon). It is freely absorbed from the tissues and results in rapid and effective haematological and clinical improvement. It is a stable non-irritant preparation of iron-dextran complex containing 50 mg of elemental iron per ml.

The iron preparation for i. m. use is more stable both *in vitro* and *in vivo*. It does not precipitate in plasma over a wide range of pH. It has a pH of 6-7 and is isotonic with tissue fluids. It is one third as toxic as saccharated iron oxide. Thirty-eight out of 40 iron deficiency anaemia patients treated with this preparation responded adequately to treatment. The total dosage varied between 1000-2000 mg, 100 mg of iron being necessary to raise the haemoglobin level by 0.34 per 100 ml. The period taken to achieve the maximum rise was four to nine weeks. The total dose was given in three to four days in hospitalized patients and twice weekly for those treated as outpatients, with satisfactory results. After a single intramuscular injection of 4 to 5 ml serum iron level attained a variable peak in one to two days and returned to about normal after six to seven days in both anaemic and healthy individuals. Urinary excretion of iron was not increased. In patients with serum levels as high as 13.8 mg per 100 ml, no toxic reactions were noted (Baird and Podmore, 1954)<sup>1</sup>.

Cappell et al (1954)<sup>2</sup> treated successfully 15 cases with intramuscular iron (200 mg every other day). Serum iron level of 600 mg in 18 hours and average regeneration rates of 3.5 - 11.3 per cent of haemoglobin per week during the first four weeks of treatment, are reported. No generalised reactions took place but local tenderness was observed. Clinical improvement occurred in one to two weeks.

Scott and Govan (1954)<sup>17</sup> treated antenatally, 50 pregnant women having iron deficiency anaemia (14 mild, 28 moderate and 8 severe) with Imferon. All responded satisfactorily. An average weekly dose equivalent to 500 mg elemental iron produced an increase of slightly more than 1 g of haemoglobin (6 per cent Haldane). Utilisation of iron was good. The results were almost identical with those obtained with intravenous iron. Many cases of mild anaemia required only two to five ml ampoules. No reactions either local or general, were encountered.

Jennison and Ellis (1954)<sup>12</sup> treated successfully 50 cases of pregnant women with Imferon.

Gaisford and Jennison (1955)<sup>8</sup> treated infants with Imferon (50 mg injections); the total dose varied, 150 to 500 mg, the average number of injections required being five. All infants improved rapidly. Anaemia of prematurity improved. Injections given deep intramuscularly were not unduly painful and no side effects were noted. It is stated that intramuscular iron therapy should not be routinely substituted for oral iron therapy, but it is valuable in severely anaemic infants and those intolerant of or resistant to oral iron preparations. Another favourable report on the use of intramuscular iron therapy in infancy is that of Wallerstein (1956)<sup>18</sup>.

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## ISLETS OF LANGERHANS—See PANCREAS

## KARTAGENER'S SYNDROME

D. Jaganatha Reddy

Dextrocardia, bronchiectasis and absent or maldeveloped frontal sinuses with sinusitis form Kartagener's syndrome. This syndrome is not very common, although mass screening procedure recently adopted as a programme in tuberculosis survey is certain to spot many of the cases which otherwise would escape the notice of the clinician. Kasliwal and Mehta reported a case who sought their medical attention for cough with expectoration of five years' duration and later noticed in him attacks of dyspnoea and palpitation. Physical examination, screening of the chest and barium meal pictures of the alimentary tract established dextrocardia with right aortic arch, bronchiectasis of the left base of the lung, liver situated on the left and dextro-position of the stomach. The electrocardiogram was characteristic of dextrocardia. On radiological examination, the frontal sinuses were absent, ethmoid air cells were rudimentary and the mastoid air cells were not visible. The authors emphasize the diagnostic importance of cyanosis and clubbing of the fingers not uncommonly associated with the condition. They also draw attention to the changes in the sinuses other than the frontal. Either in bronchiectasis or in dextrocardia the association of the two must be eliminated.

Divekar reported five cases of Kartagener's syndrome and the age of the patients ranged from 7 to 23 years. Fever, recurrent attacks of cough with expectoration and cold were common to all the cases. In all of them the existence of bronchiectasis was proved on bronchography. Clubbing of the fingers was noticed. Three patients gave a history of consanguinity in their parents. In one, transposition of the viscera was not seen but instead, congenital heart lesion was present and in another imperforate anus at the time of birth was said to have been observed. Bronchiectasis in Kartagener's syndrome is believed to be due to congenital weakness of the bronchial wall and secondary infection leading to obstruction.

Devadatta from Vellore reported a typical case of Kartagener's syndrome in a male aged 30 years, confirmed by skiagraphic and electrocardiographic data and bronchiectasis localised to the left middle and lower lobes. The affected portion was resected. The author drew attention to the case reported by Raman et al and stressed on the alarmingly high incidence of bronchiectasis in dextrocardiacs compared to normal individuals.

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### LARYNX AND ADJACENT PARTS, CANCER OF

S. N. Sarma

In recent years cancer has ascended in the ladder of the greatest killers. Cancer of the larynx is no longer a rare disease. It was but vaguely known in olden times. In 1790, Morgagni referred to two of Valsalva's cases. Laborgne (1953) traced the history through 1833 to 1876 when gradually more cases were being detected, with Gracia's invention of the laryngoscopic mirror. He pointed out the difficulties in comparing observations for lack of uniform methods in reporting. Lindsay and Ironside (1955) stated that there was still considerable confusion as to the classification of tumours of the larynx. The most widely adopted classification is that of Krishaber and Isambert. It is more than 70 years old but applied by different authors in different ways, leading to confusion. The International Union Against Cancer is trying to evolve an agreed classification.

**Incidence.** As with cancer in other parts of the body, the incidence of cancer of the larynx varies in different parts of the world. Baltzell and Putney (1954), found from their study of 1498 cases of laryngeal cancer during the period 1928-1953, at the bronchoscopic clinic of Jefferson Hospital, that there was a positive increase in the incidence and stated that the disease was found seven times more frequently in the past ten years. This increased incidence paralleled that of lung cancer, but did not approximate to the phenomenal increase in bronchogenic carcinoma. Kennaway and Kennaway (1954) from their study of the mortality figures in England and Wales for the preceding 20 years, stated that in contrast to the well-known large increase in the death rate due to lung cancer, there had been little change in the death rate from cancer of the larynx. He further added that :

1. Cancer of the lung and the larynx in the males showed similar relation to urban and rural conditions;
2. Cancer of the larynx was four times more common in men than women;
3. In men, cases of intrinsic cancer were hardly twice as common as those of extrinsic, whereas in women cases of extrinsic cancer were four times as common as intrinsic;
4. In men intrinsic cancer was 13 times that in women, and extrinsic about twice as frequent.

Wynder, Bross and Day (1956) stated that the incidence of laryngeal cancer in the U.S.A. and Europe was estimated to be between three to four per 100,000 population. The incidence has been particularly high in India, where in a series of 5640 cancer cases studied at the Tata Memorial Hospital, Bombay, 12.1 per cent cases were of the larynx. From their study, they found an increase in the incidence of cancer of the larynx in the U.S.A., as compared to the incidence in England where there has not been any appreciable change.

Khanolkar (1950) observed that the first survey of malignant disease in India was carried out by Nath and Grewal from hospital records of most of the principal medical centres in India and it showed that all varieties of malignant tumours had been seen and the opinion that they were not so common in this country had not been correct. He presented statistics from the Tata Memorial Hospital which showed that cancer of the larynx constituted 12.1 per cent of all cancer cases. It was an impressive group in men of fourth to seventh decades of life in Bombay. Seventy-six per cent of the laryngeal cases were of the extrinsic variety.

Sarma (1951, 1952, 1953, 1954) working in the Eastern part of India, at the Assam Medical College Hospital, reported that cancer of the larynx formed 50 per cent of the cancer cases at this hospital, and that the Assamese people were more susceptible to its occurrence. He compared available figures from the U.S.A., the U.K. and India and stated that nowhere else was the incidence of laryngeal cancer so high as in Assam. Available figures put it as the highest amongst the Assamese people. He found large number of cases below 30 years of age, the largest number between 40 and 50 years; the youngest case was 9 years old. He also found that practically all (i.e. 98 per cent) of the cases were of extrinsic variety and only 2 per cent were of the intrinsic variety.

**Aetiology:** Sadowsky (1953) from his study concluded that his data considered together apparently warrant an association of cigarette smoking with incidence of laryngeal cancer. Kennaway and Kennaway (1954) stated that the increased incidence of lung cancer had been attributed to greater consumption of tobacco but the constancy of the mortality from cancer of the larynx found in their study suggested that smoking had no carcinogenic effect on the larynx.

Hence some other reason must be sought for. Maxwell (1955), following his survey reported that there had been a great increase in the incidence of lung cancer, but during the same period there was no increase in the incidence of laryngeal cancer. The increase in lung cancer was attributed to increased tobacco smoking. He discussed how despite the increase in smoking, there was no increase in laryngeal cancer, though the concentration of inhaled carcinogenic substances would be much more in the larynx. He doubted if smoking was a cause of laryngeal cancer and suggested to search for some unsuspected factors which may be responsible. As stated above, Sarma (1953-54) had pointed out that the incidence of laryngeal cancer was very high in Assam and that 98 per cent of cases had the extrinsic type. The part of the larynx involved in this variety is physiologically concerned in the act of swallowing and hence, the causative factors should be sought for in the food habits of the Assamese. Sarma has suggested that the type of betel nut commonly eaten in this part of India may be a causative factor. He has discussed in detail the characteristics of the betel nut used in Assam, by the Assamese people and has pointed out how it differs from other varieties used in the rest of India. He has also pointed out that the incidence has been low in those parts of India like the Punjab, where people are not generally used to chewing betel nut. Finally Sarma (1956) concluded from his survey that there is a definite close correlation between the high incidence of cancer of the larynx in Assam and the betel nut chewing habit of the population here.

Sanghvi, Rao and Khanolkar (1955), stated from their study in Bombay, that the habit of chewing *pan* was associated with cancer of the oral cavity, the habits of smoking and chewing tobacco with cancer of the hypopharynx and base of the tongue, whereas the habit of only smoking, with cancer of the oropharynx and the oesophagus. Wynder, Bross and Day (1956), stated from their study that unlike extensive literature on lung cancer, relatively few reports were available regarding significant environmental factors in the incidence of laryngeal cancer and still fewer were authentically based on statistical evidence. The evaluation of various aetiological factors in the incidence of laryngeal cancer for white American men, showed most of the factors, except alcohol and tobacco, to have very little importance in the incidence of this disease. Regarding Indian data available from Bombay, it is stated that laryngeal cancer was higher in those who smoked *bidi* and chewed *pan*. The observations suggested that chewing itself may be associated with extrinsic type of laryngeal cancer, but could not be determined on merely such data alone, as majority of those cases were used to both chewing and smoking. They further stated that in Sweden extrinsic laryngeal cancer in women showed a relation to dietary deficiency.

An editorial in the B.M.J. (1956) discussed this problem and stated that it would be unjustifiable to conclude merely from vital statistics that there was anything contradictory in the observations that pulmonary and laryngeal cancer were both produced to some extent by tobacco. Cancer of the larynx is not one disease, but a group of diseases having in all probability varying aetiology.

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## Leishmanoid, Dermal and Oriental Sore, Radiotherapy in

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## LEISHMANIASIS, POST-KALA-AZAR DERMAL

K. C. Sahu

There has been a marked increase in the number of cases of post-kala-azar dermal leishmaniasis (DL) following the outbreak of kala-azar in Eastern India. Records of 1000 cases attending the kala-azar outpatient department of the School of Tropical Medicine, Calcutta, have revealed some interesting facts.

It was noted that relatively larger proportion of kala-azar cases developed dermal leishmaniasis towards the end of an epidemic and subsequently than during the epidemic years. This indicates that there is a rise of immunity against the visceral disease but not against the dermal conditions at the end of an epidemic of kala-azar.

Specific treatment of kala-azar, however, intensively administered and the use of the most effective drugs, does not prevent the development of DL, though the visceral disease is cured. Treatment of this disfiguring condition is still not very satisfactory.

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## LEISHMANOID, DERMAL AND ORIENTAL SORE, RADIOTHERAPY IN

K. C. Sahu

Ninety cases of dermal leishmanoid (DL) and 21 cases of oriental sore were treated with radiotherapy. Two types of DL were treated, viz. the nodular and hypopigmented macular types. All cases of DL were given a total of 300-350r divided into six doses, bi-weekly. The factors used were 100 KVP, 5mA., 1 mm AL filter, 30 cm distance. A few oriental sore cases were given harder rays by increasing the intensity and altering the filtration.

The hypopigmented areas grew darker during the course of treatment due to photosensitive effect on the skin, but hypopigmentation returned as soon as the darkening was over.

The nodular lesions regressed very slowly if at all when compared with the extent of treatment. Radiation alone in the region of 2000r failed to produce any beneficial effect on oriental sore.

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## LEPRA BACILLUS, CULTURE AND TRANSMISSION IN MONKEYS

K. C. Sahu

M. leprae have been successfully cultivated in a medium containing M. phlei, Lowenstein-Jensen salt solution and whole eggs.

Leprosy has been successfully transmitted to monkeys by introducing the infective materials, culture and suspension of ear lobe pieces from leprosy patients, through the left ulnar nerve.

The manifestations of leprosy were as follows: (i) Thickening of the ulnar nerve, (ii) presence of acid-fast bacilli in various organs far remote from the place of inoculation, (iii) marked fibrosis in nerves especially the inoculated ones and in the spleen, (iv) reddish-brown lesions over the nose and, (v) claw hands on the same side as the inoculated nerve; this was however well marked in one monkey only.

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**LEPROSY, CHEMOTHERAPY RETARD OF—See CHEMOTHERAPY RETARD OF LEPROSY**

**LEPROSY, CORTISONE AND CORTICOTROPHIN IN—See CORTISONE AND CORTICOTROPHIN IN THE REACTIVE EPISODES OF LEPROSY**

**LEPROSY, FACIAL PARALYSIS IN**

K. C. Sahu

The present discussion refers to a series of 10 cases of facial paralysis due to leprosy who came under my observation. The aetiology of facial paralysis is varied. Leprosy has been hardly described as the cause of facial paralysis in the literature or text-books of medicine. It should be kept in mind when investigating such a case. In my series there was no neuralgic pain nor sensory disturbance in the area supplied by the facial nerve. The affected skin area showed macular eruption in two cases but in the rest, small pigmented areas were found. The cases have often been missed for cellulitis or erysipelas or considered as due to some underlying conditions like sinusitis, etc.

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**LEUCODERMA, EMETINE IN THE TREATMENT OF**

K. C. Sahu

Leucoderma is an annoying, disfiguring disease in the tropics. The cause of functional disturbance of melanoblasts is unknown. In India, it has been observed that in the majority of cases there is some definite evidence of intestinal infection, specially not infrequently it is associated with chronic intestinal amoebiasis. In these cases, perhaps with the change in the bacterial flora of the gut associated with amoebic infection, the precursors of melanin are absent and hence leucoderma results. In 10 cases, where there was neither clinical nor laboratory evidence of amoebiasis, a course of emetine hydrochloride, one gr, given every alternate day for 10 injections, produced very good results and most of the patches of leucoderma vanished.

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**LEUCODERMA, PITUITARY TREATMENT OF**

K. C. Sahu

Pituitary gland therapy was tried in 50 cases of leucoderma which did not yield to the routine treatment. Fresh pituitary gland was taken from young goats or sheep, emulsified in Ringer's solution and was immediately injected intramuscularly deep into the gluteal muscles once a week for five to eight weeks. Improvement was noticed in three to four weeks. Six cases were completely cured, 21 improved partially and 23 did not improve. The failure might be due to incomplete treatment or it is possible that there might be some other cause of the disease besides the pituitary MSH hormone deficiency. Appearance of pigment on the lips, palms, soles and sides of the feet was remarkable.

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**LEUCOTOMY**

N. S. Vahia

There is a difference of opinion regarding the place of leucotomy in the treatment of mental illnesses. This treatment was advised commonly for patients who were chronically disturbed. Nowadays tranquillizers have been found to be useful in such a high percentage of chronically disturbed patients, that leucotomy is not considered necessary for most of them. It might be noted, however, that some workers prefer leucotomy to tranquillizers (Cheng and others<sup>2</sup>, Petri and LaBeau<sup>13</sup>).

*Indications* : P. Hoch<sup>9</sup> considers that psychosurgical procedures can be therapeutically effective in cases of pseudoneurotic forms of schizophrenia, who have failed to benefit from other treatments. In his series there was a significant improvement in 65 per cent of 37 patients and improvement was maintained after 3 years follow up. Leucotomy is also indicated in cases of

## Leucotomy

psychoneuroses that do not respond to psychotherapy and other procedures. It is also useful for depression which is resistant to other conservative treatment (Freeman<sup>3</sup>). Grantham<sup>7</sup> found it useful in painful and psychosomatic illnesses like ulcerative colitis and tuberculosis with mental changes. Leucotomy is not useful for psychopathic personality and is not efficacious in disturbed mentally retarded children.

It is considered that to obtain satisfactory results with leucotomy, it would be desirable to give the treatment early, because in advanced psychosis the personality disorganisation being great the end results are less satisfactory. It is suggested that if a patient does not respond to conservative line of treatment, leucotomy should be advised before the patient deteriorates. Mettler<sup>11</sup> found inverse relation between the extent of deterioration and chances of discharge from the hospital. Schizophrenic patients responded well if operated upon in the first two years of hospitalization.

**Techniques:** Various modifications of standard leucotomy have been recommended by different workers to produce minimum damage and maximum therapeutic response. Bimedial leucotomy is considered to be more efficacious and less damaging by Paul<sup>12</sup>. Transorbital leucotomy is considered to be the treatment of choice in early cases by Freeman<sup>3</sup>, who believes that standard leucotomy should be reserved only for those cases that do not respond to transorbital leucotomy. Thalamotomy produces high incidence of disorientation and memory loss. Electrocoagulation of basal medial quadrants of the frontal lobes has been found to be useful by Ayd<sup>1</sup>. Fry<sup>5</sup> produced focal lesions in the depth of the brain with the help of ultrasound in animals. Lindstrom<sup>10</sup> found prefrontal ultrasonic irradiation a good substitute for lobotomy, because of the absence of complications and minimum structural alterations in the path of the sound beam, suggesting that ultrasonic irradiation caused minimum damage. It is possible that the technique might be very useful in doing pin point damage to that area of the cerebrum which would be found to be the most important in the treatment of mental illness.

**Results:** As there are various techniques for leucotomy and as different yardsticks have been used by different workers, it is somewhat difficult to compare the long term results of leucotomy cases.

Schwarz<sup>15</sup> on a 6-year follow up of leucotomy cases found that out of 38 schizophrenic cases only 9 had been discharged. He believed that these unsatisfactory results in his series might be due to lack of follow up, psychotherapy and rehabilitation. Tow<sup>17</sup> performed a battery of intelligence and personality tests before and after a standard leucotomy in 36 patients. He found impairment in the personality function particularly in power of abstraction and synthesis, lack of worry over failures, etc. He concluded that there was a lower level of activity after operation in various aspects of the patient's intellectual life. Freyhan<sup>6</sup> obtained a high rate of failure and believed that therapeutic benefits were generally rather limited. Pippard<sup>14</sup> is optimistic regarding the value of leucotomy in mental illness, but advises caution, as leucotomy is potentially harmful and he does not consider it advisable as a last resort of a therapist.

On the other hand, Greenblat and Soloman<sup>8</sup> felt that if everything that a community could offer had been done for a psychotic or a chronically neurotic patient and if he did not show improvement for 2½ to 3 years, leucotomy should be considered. In a well controlled series of severe chronic schizophrenia cases treated with prefrontal leucotomy, they found that operated patients showed more tendency to improve. Paul<sup>12</sup>, who followed up his cases for 5 years, using 3 types of leucotomy—bimedial, full bilateral, and unilateral, found that the maximum improvement with minimum personality deterioration was noticed in bimedial leucotomy. 54 per cent of his patients were working full time. Gashes and LaBeau<sup>6</sup> found excellent results in 70 per cent of their cases. Stallworthy<sup>16</sup> who studied 154 patients, found improvement in 35 per cent of schizophrenics, 75 per cent of melancholia and all the neurotics, of such a degree that they were discharged from the hospital. Amongst them about half of schizophrenics and all the melancholics and neurotics were self-supporting. A 2½ years follow up showed no variations in the symptoms. Freeman<sup>3</sup> recently reported a follow up study of 3000 patients from 1 to 20 years. He compared the results in three different categories—(1) prefrontal leucotomy—transorbital leucotomy, (2) private patients—state hospital patients, (3) according to personality reaction type. His studies revealed that after prefrontal leucotomy about 70 per cent of schizophrenics, 80 per cent of manic or depressive and 90 per cent of psychoneurotic

patients were functioning outside the mental hospital in 5-10 years' time. The results were much more gratifying in private than in state hospital patients. According to him transorbital leucotomy is safer, more effective (except in cases of schizophrenia with hallucinations) and far more useful than prefrontal leucotomy. He found more than one operation useful if the first one failed.

**Conclusions :** As long as the mind and brain relationship has not been finally established, the advisability of a brain operation for mental illness will continue to be a matter of opinion. It might be noted that in Russia leucotomy is prohibited because it is believed that the rationale of the treatment is questionable and the results are unsatisfactory.

In Europe and America, particularly because of the recent advances in chemotherapy, the place of leucotomy in psychiatry at present is being re-evaluated. The present consensus of opinion seems to be that if the operation is considered advisable, it should not be delayed too long. Leucotomy is likely to be most useful in cases of severe depression and in psychoneurosis resistant to all other treatments. It is also of value, but to a less extent, in some forms of schizophrenia, like pseudoneurotic type. While advising this procedure, the possibilities of changes in the personality have to be considered and therefore conservative leucotomy, like transorbital or bimedial might be considered first. More conservative modifications of leucotomy like the use of ultrasonic sound will have to be tried extensively before its final place in the treatment of mental illnesses has been established.

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**LIGNAC-FANCONI SYNDROME—See CYSTINURIA AND CYSTINOSIS**

#### LIVER FUNCTION TESTS, POST-MORTEM

V. C. Anguli

In previously published work Naumann demonstrated the value of post-mortem chemical tests as aids in diagnosis, and certain techniques and interpretations were outlined. These tests



## Liver Function Tests, Post-mortem

were helpful (1) in the diagnosis or confirmation of diabetes mellitus or diabetic coma (by post-mortem determination of glucose and carbon dioxide, and by detection of acetone, in cerebrospinal fluid or blood from the left side of the heart), as well as, (2) in the diagnosis or confirmation of uraemia or uraemic coma (by determination of urea, creatinine, and carbon dioxide).

In this study certain tests of hepatic function were performed post-mortem on serum and urine, with the purpose of correlating such findings with gross and microscopic changes in the liver, and of interpreting the latter in terms of hepatic function.

*Method and Material:* Blood was collected at autopsy from the inferior vena cava approximately 10 hours after death and was allowed to settle or clot in the refrigerator for 24 hours. The supernatant plasma or serum, which was usually clear and only moderately haemolyzed, was withdrawn and centrifuged. Serum obtained by centrifuging whole post-mortem blood soon after removal from the body was more haemolyzed, and this interfered with most of the tests. On the other hand, settling for 24 hours at 3 to 8° C caused some lowering of the concentration of cholesterol esters and alkaline phosphatase, and some increase in the degree of cephalin flocculation. Comparative determinations in blood from the left and right sides of the heart did not reveal sufficient differences to justify working with the relatively small samples available from the left side of the heart. The urine was obtained either by catheterization or puncture of the exposed bladder.

**Summary.**—1. The following tests for hepatic function were performed on post-mortem material from 131 patients: the content of bilirubin, cholesterol and cholesterol esters, albumin and globulin, and alkaline phosphatase in serum; cephalin flocculation and thymol turbidity of the serum; the content of urobilinogen, urobilin and bilirubin in the urine.

2. Normal values were established for tests performed on an average of 10 hours after death in patients free of disease of the liver and of conditions known to affect the results of the tests. In such patients the values for bilirubin, total cholesterol, and proteins in the serum, and those for urobilin and bilirubin in the urine, corresponded closely with the values usually regarded as normal during life.

3. Post-mortem changes, including haemolysis, caused a decrease in cholesterol esters (40 per cent of total), an increase of the cephalin flocculation (2 to 4 plus), and a decrease of urobilinogen (under 0.4 unit) by oxidation to urobilin.

4. Post-mortem results of determinations of serum proteins, total cholesterol, alkaline phosphatase and thymol turbidity were in fair agreement with those found antemortem, but did not correlate closely enough with disease of the liver to be of value in individual cases.

5. The determination of bilirubin in the serum and of urobilin in the urine were the most reliable post-mortem tests for hepatic function because of absence of post-mortem changes, good agreement with ante-mortem values and reasonable correlation with abnormality of the liver.

6. Post-mortem values for bilirubin in the serum and urobilin in the urine were helpful in establishing damage of the liver as a contributory factor causing death, although the anatomic changes in the liver were absent or slight, and also in interpreting the severity of disease of the liver in terms of hepatic dysfunction.

7. Several instances of unsuspected jaundice were detected post-mortem by finding an increase of total bilirubin from 2.1 to 5.4 mg per 100 ml of serum. The livers of these patients had passive or active congestion, cloudy swelling, fatty changes, and infiltrations of lymphocytes.

8. Massive necrosis of the liver from hepatocarcinoma or subacute yellow atrophy was associated with marked bilirubinaemia, moderate urobilinuria, low levels of serum albumin and total cholesterol, a high level of alkaline phosphatase, and increased thymol turbidity of the serum. Such results with the combined tests for hepatic function were interpreted as indications that hepatic failure was a primary or a major, contributory cause of death.

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## LOW SODIUM DIET—See DIET, LOW SODIUM

## LUNG ABSCESS

D. Jaganatha Reddy

With the functioning of thoracic surgery units in the teaching hospitals in India, more cases of lung abscess are clinically recognised and surgical treatment of the cases has conferred on these patients a normal span of life. Sanghvi recently reviewed clinicopathological data of 40 cases of lung abscess under his care for the period 1953-1955. Malignant disease and tuberculosis were excluded. Maximum incidence was observed in the age group of 20 to 40. Except one, all were males and over 75 per cent of them represented low income groups. The incidence paralleled the high incidence of respiratory infections and was mostly seen in the months of October and November and December to March. Twentyfour cases had abscess in the right side and 12 in the left.

Wig in 1951, reporting 28 cases of lung abscess observed only three cases below 20 years of age and 75 per cent of them were between 21 to 50. Pneumonia as an antecedent condition was noted in 17 cases and in another 7 cases upper respiratory infection associated with exposure and strenuous work was noted. None in the series could be ascribed to post-operative complication. Dental sepsis in a small percentage of cases was observed in both the series but the same incidence of dental sepsis was noticed in a control series not suffering from lung abscess and as such of doubtful causal significance. Maxwell pointed out the absence of tonsillectomy and dental sepsis in his series and so also in Brock's series. Pneumonia and infection of the upper respiratory tract form the commonest causes of lung abscess where dental sepsis has little aetiological significance.

Karai and Basu reported 14 cases of so called clinically diagnosed lung abscess, ten of which were pyogenic, two of tubercular origin, one of infected cyst and another following carcinoma. Three died and the remaining showed either improvement or permanent cure by open drainage, conservative treatment or lobectomy.

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## LUNG ABSCESS, TREATMENT OF

John G. David

In the management of lung abscess one must be familiar with the mode of infection, the causative organisms and the distribution of the abscess in the lung tissue.

**Mode of infection.**—Though not definitely proved, it is believed mainly due to aspiration of the infected material causing emboli or due to bronchial or bronchiolar obstruction. Wolcott and Murphy<sup>7</sup> explain that infection plus infarction lead to tissue necrosis and suppuration.

The precipitating causes according to them fall under five broad groups :

1. Unconsciousness from any cause—trauma, anaesthesia, epilepsy, drug narcosis, insulin shock, diabetic coma, alcoholic intoxication ;
2. Acute infections, pneumonias of pyogenic or viral origin, and severe upper respiratory tract infections ;
3. Foreign body aspirations, teeth, tonsillar tissue, peanut-shells, beans, etc. ;
4. Penetrating wounds of lung tissue resulting from various causes ;
5. Idiopathic, i.e. cases in which no clear-cut cause is known.

Sanjivi<sup>5</sup>, in his study of 52 case-reports, stated that only a small number of bronchial emboli proved to have been secondary to inhalation of material from upper respiratory passages. He considers the origin as being meta-pneumonic in the absence of demonstrable causes. In his series 2 cases followed tonsillectomy, 2 after electroconvulsive therapy and one after removal of fishbone from the oesophagus.

Sanghvi<sup>4</sup>, in his analysis of 40 cases for aetiology and localisation of lung abscess reports pneumonia and infection of upper respiratory tract as common causes and dental caries had little part in the aetiology.

Bhaskara Reddy and Mohan Reddy<sup>1</sup> from their study based on autopsy records of 34 cases, from 1925 uptodate show the aetiological factors in the causation as follows :—Pneumonia-23, pyaemia-5, aspiration-5 and amoebiasis-1.

## Lung Abscess, Treatment of

From these studies it will be seen that pneumonia and infection of the upper respiratory tract form the main causes which may be precipitated by one of the various factors mentioned above.

**Causative Organisms.**—From various reports of study from India and other countries it is seen that *Streptococcus viridans*, *staphylococcus*, *pneumococcus* and *micrococcus catarrhalis* are the main causative organisms<sup>1, 4, 5, 7</sup>. Sanjivi reports on two cases of *Bacillus coli* infection and one case of *B. faecalis alkaligenes* from his study. Gopinath and Thomas<sup>2</sup> report of one case in which *S. typhosus* was isolated from the aspirated pleural fluid following lung resection for abscess among 100 cases.

Carcinoma as an aetiological factor in lung abscess is increasingly common and should be considered in the diagnosis as pointed out by Waterman and Domm<sup>4</sup> from their studies.

Amoeba was found in one case among 34 cases studied by Bhaskara Reddy and Mohan Reddy<sup>1</sup>.

**Distribution of Abscess in the Lung.**—The right lung is more commonly affected than the left and the lower lobe is more often affected than the upper lobe.

Sanghvi, in his studies of 40 cases for localisation of lung abscess, found the right upper lobe commonly involved and the apical segment of left lower lobe was the commonest segment involved. The anterior segment of upper lobe and right middle lobes were more frequently involved than in other reported cases.

Bhaskara Reddy and Mohan Reddy<sup>1</sup> from their study of 34 autopsy cases report the distribution as, right side 16, left side 9 and both sides 9. According to them the lower lobes in both the lungs seem to be affected more frequently than the upper lobes and they found only 3 cases affecting the middle lobe.

In Lockwood's figures as quoted by Sanjivi<sup>5</sup> the right side was involved in 71.5 per cent and the left side in 29.5 per cent of cases. In his own series of 52 cases right side was involved in 62 per cent and left side in 38 per cent of cases. Lockwood's series shows 35 per cent of upper lobe, 60 per cent of the lower lobe and 5 per cent of middle lobe involvement, while in Sanjivi's series, upper lobes were involved in a little over 50 per cent, the lower lobes in 34 per cent, and the middle in 15 per cent.

From these studies one can conclude that in the majority of the cases the right side is more commonly involved than the left and the lower lobes more than the upper. Only Sanjivi<sup>5</sup> reports the involvement of upper lobes in greater proportion to others.

**Treatment.**—Postural drainage is still considered as an important factor in the management of lung abscesses and is used as a conservative method along with selected antibiotics. Several workers claim very good results from this combination as will be seen later. The position of the patient differs in relation to the affected lobe and segment of the lung tissue and hence the importance of the study of the distribution of abscesses.

Surgical drainage once widely used is seldom practised nowadays.

Endocavitary aspiration used for the first time in 1938 by Monaldi<sup>3</sup> in the treatment of pulmonary tuberculous cavities had been tried by him and his associates in lung abscess. Monaldi<sup>3</sup> in his study of 38 cases reported 33 recoveries (87 per cent) and only five failures which were due to fatal haemoptysis (1 case), inefficient treatment (1 case) and relapse in chronic case with bronchiectasis (3 cases).

Endocavitary aspiration was followed by local antibiotic applications during the first week. The treatment lasted from 15 days to 3 months.

Wolcott and Murphy<sup>7</sup>, in their study of 65 cases, divided them into three groups : (i) sulphanilamide period, 1941-44, 19 cases, (ii) penicillin period, 1944-52, 29 cases and (iii) antibiotic period, 1952-56, 17 cases, and reported their mortality rate (medical and surgical combined) as 31.5 per cent, 17.2 per cent and 0 per cent respectively. In the same study they also compared the mortality rate of 21 cases treated with drainage as against 16 cases of resection, which was 38 per cent in the former and 6.3 per cent in the latter. They also claim better results with Tryptar, an enzymatic debridement by aerosol therapy.

Recent workers from India and other countries claim good results with conservative treatment consisting of combination of penicillin and postural drainage.



PLATE VI

FIBROSARCOMA OF LUNG



FIG. 1

*Reduction skiagram of the chest shows diffuse opacity in the left lung and circumscribed shadow in the right.*



FIG. 2a

*Massive homogenous white tumour of the upper half of the left lung and similar tumour mass between the middle and the lower lobes of the right lung.*



FIG. 2b

*Photomicrograph illustrates sarcomatous tissue of the tumour bordering the lung parenchyma, (H&E x40).*



FIG. 3

Waterman and Domm<sup>6</sup> studied 134 cases which they divided into two groups, (i) pre-antibiotic-60 and (ii) post-antibiotic-74 and reported the mortality as follows :

<i>Type of treatment</i>	<i>No. of cases treated</i>	<i>No. died</i>	<i>Mortality percentage</i>
1. Conservative treatment			
Pre-antibiotic	60	14	23.3
Post-antibiotic	74	3	4.0
2. Drainage treatment			
Pre-antibiotic	16	2	12.5
Post-antibiotic	15	3	20.0
3. Resection			
Pre-antibiotic	14	4	28.6
Post-antibiotic	41	1	2.4

In conservative series, those cases which failed to improve and later underwent resection are omitted.

From this study it will be clearly seen that the judicious use of antibiotics has indeed brought down the mortality rate in conservative and resection series. In most of the cases penicillin was given by parenteral and/or aerosol route. The latter was given by means of oxygen pressure nebuliser after bronchoscopy in doses of 25,000 to 50,000 units every three hours. They claimed that none of the usual antibiotics such as Aureomycin or chloramphenicol, were found as effective as penicillin by aerosol therapy.

Good results with penicillin were also reported by Sanjivi and others<sup>1, 4, 5</sup> in India<sup>1</sup> and Waterman and others<sup>6</sup> from other countries. Three to 5 lacs units of penicillin were given every 3 hours day and night for a minimum of 5 weeks. The improvements were very marked in acute cases. This can be clearly understood when one realises that most of the organisms cultured from the sputa from cases of lung abscess are sensitive to penicillin.

Supportive treatment in this series was good nursing, proper nutrition, bronchoscopy and drainage and postural drainage.

**Conclusion.**—The management of lung abscess has changed a great deal after the discovery of antibiotics. Acute cases respond well to penicillin. With postural drainage and selected antibiotic and enzymatic aerosol debridement nearly all lung abscesses may be either cured or brought to an optimal condition for resectional therapy. It must also be emphasised that bronchoscopy and drainage play an important part in the treatment of lung abscess.

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#### LUNG, FIBROSARCOMA OF

*D. Jaganatha Reddy*

Sarcomas of the lung are rarely reported. Reddy et al reviewed the literature briefly and emphasised the rarity of pulmonary sarcomata in contrast to the high incidence of carcinoma. While reporting a case of primary sarcoma of the lung the authors stress the importance of necropsy in these cases to exclude primary growth elsewhere.

A male patient aged 50, sought medical aid at the Guntur General Hospital for dyspnoea of 15 days' duration. The mediastinum and the trachea were shifted to the right and aspirated pleural fluid did not disclose any malignant cells. Skiagram of the chest showed opacity on the left side and a circumscribed circular shadow on the right (Fig. 1). The patient expired 18 days later. Necropsy disclosed a dense homogenous white mass covering the left lung and a nodule of similar colour wedged in between the lower and middle lobes of the right lung (Figs. 2a, 2b). Other organs were normal. Sections of the tumour mass were composed of spindle cells with malignant features blotting in places the lung structure. The tumour cells

## Lupus Erythematosus Disseminatus

were seen to be arranged in whorls. Necrosis, haemorrhage and calcification were the significant findings (Fig. 3). The interlobar lymph nodes were completely replaced by tumour tissue. The authors suggest that the tumour was arising from the interstitial tissue of the lung. The morphology of the tumour should guard the clinician from drawing wrong conclusions in the absence of a tumour on endoscopy.

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## LUNG, MALIGNANT EPITHELIAL TUMOURS OF—See MALIGNANT EPITHELIAL TUMOURS OF LUNG

### LUPUS ERYTHEMATOSUS DISSEMINATUS

*D. Jagannatha Reddy*

Dermatologists and physicians are particularly aware of the fact that lupus erythematosus disseminatus presents diverse clinical manifestations and that the clinical recognition of the same is not always easy. This is because of the involvement of several viscera. Aetiology of the condition is still obscure. The disease is characterised by remissions and relapses. The demonstration of "L.E. cell" by Hargreaves has added an important milestone on the way to understanding of the disease, though this phenomenon is not considered pathognomonic of lupus erythematosus disseminatus. In the absence of the typical cutaneous lesions, the damage caused to kidneys, lungs, heart, etc., is very often not recognised during life. Reddy et al record the necropsy findings of such a case, the condition having been missed during life.

The myocardium showed extensive fibrosis and collagen deposition (Fig. 1). The lungs showed circumscribed zones of consolidation with surrounding areas apparently being normal. Sections from these firm areas disclosed young innumerable capillaries surrounded by varying thickness of collagen and at the periphery bordered by multilayered mononuclear cell collections (Fig. 2). Arteriosclerotic changes were also noticed. Hyaline thrombi were seen filling the capillaries. Sections of the kidneys showed thickening of Bowman's capsule and heavy collagen deposition of the glomerular capillaries simulating the appearance of "wire-loop capillaries", characteristic of lupus erythematosus disseminatus (Fig. 3). The authors attribute the peculiar histological findings observed by them in the lungs in association with the changes in renal glomeruli to allergic process.

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### MALIGNANCY, MEDICAL TREATMENT OF

*M. N. Guruswami*

During the last decade or two, serious attempts have been directed to learn the biochemical mechanisms occurring in normal and malignant cells, the mode of action of many chemotherapeutic agents and to find physical, chemical and biological agents exerting specific curative effects in malignant diseases. It is not possible to attain "therapia sterilizatio magna" in malignancy as in bacterial infections. A few resistant cells always survive. Unlike bacterial cells, leukaemic cells are not treated by body defence mechanisms as foreign. Hence they persist and multiply until the disease attains its full strength. The best that can be done is to protract life and possibly postpone the development of resistance to a limited extent to chemotherapeutic measures (Witts, 1954)<sup>1a</sup>. However, in most cases, only palliative measures are possible.

Some advances in the following malignant diseases will be discussed : 1. Leukaemias, acute and chronic ; 2. Hodgkin's disease ; 3. Polycythaemia vera ; 4. Cancer of the thyroid ; and 5. Malignancy of breast and prostate.

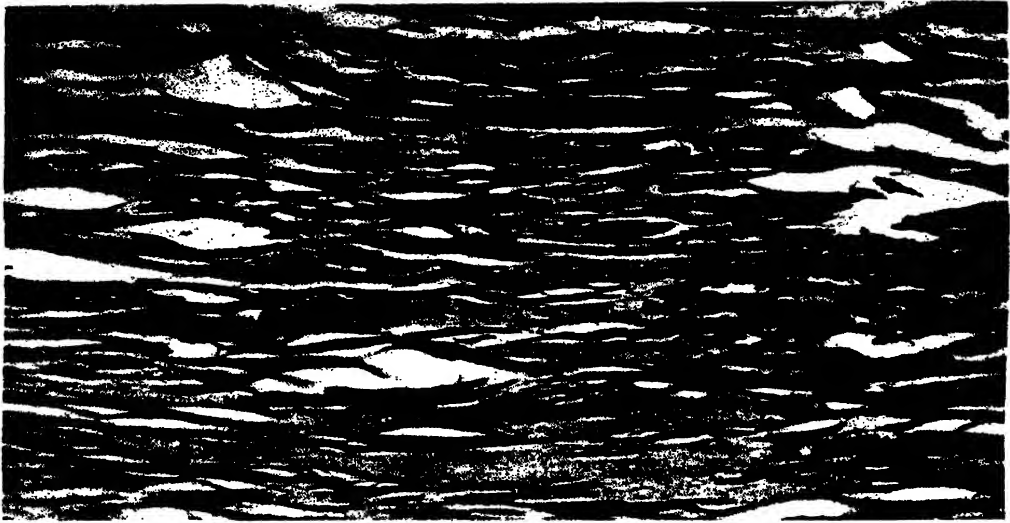
*Acute Leukaemia* : The treatment may be specific and non-specific.

*Non-specific* : measures include blood transfusion, control of infection by antibiotics, relief from pain, etc.

*Specific* : antileukaemic measures include X-ray irradiation which is not always beneficial and sometimes may be deleterious ; this method is used only in rare instances.

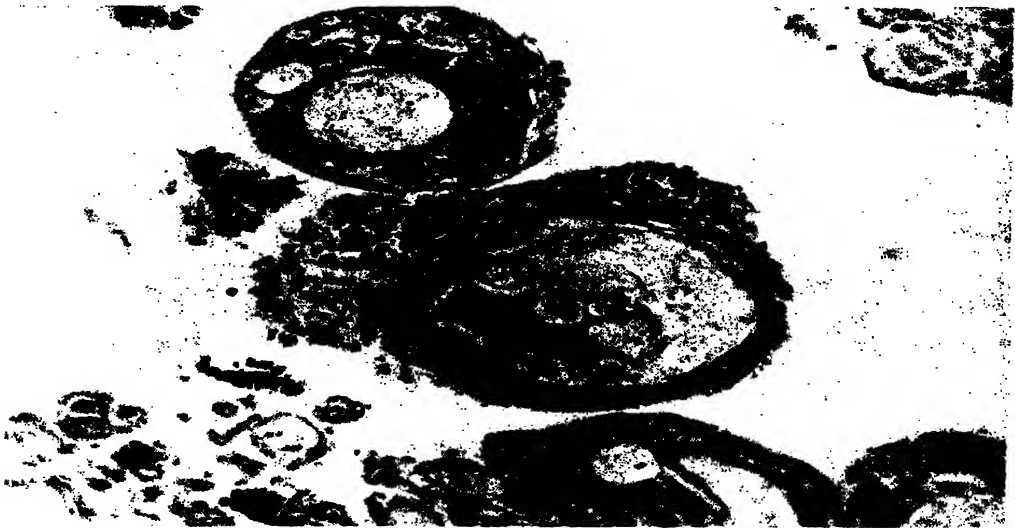
*PLATE VII*

**LUPUS ERYTHEMATOSUS DISSEMINATUS**



**FIG. 1**

*Photomicrograph illustrates extensive collagen degeneration of the myocardium and occasional fragment of surviving myofibrils (H&E x60).*



**FIG. 2**

*Photomicrograph illustrates multiple vessels bordered by collars of collagen tissue and mononuclears in the lung (H&E x100).*



*PLATE VIII*

**LUPUS ERYTHEMATOSUS DISSEMINATUS**



**FIG. 3**

*Photomicrograph illustrates thickening of the Bowman's capsule and characteristic "wire loop" glomeruli (H&E x100).*

**Folic Acid Antagonists:** Aminopterin and amethopterin are useful chiefly in lymphocytic leukaemia in children ; occasionally all types will respond to them even in the adults. The daily dose of these drugs is 0.5 to 1 mg of aminopterin and 2.5 to 5 mg of amethopterin. Severe bone marrow depression with leucopenia and thrombocytopenia may occur. Also, alopecia, stomatitis and extensive gastrointestinal ulceration with bleeding may result. Folinic acid (5-10 mg daily) may counteract these effects. It is wise to stop the drug when stomatitis appears.

**Purine Antagonists:** 6-mercaptopurine (Purinethol, an antagonist of guanine and hypoxanthine). The daily oral dose is 1 to 1.5 mg/lb body weight. The drug is well-tolerated and less prolonged in its effect on the bone marrow than are the antifolic acid compounds. Severe bone marrow depression does not occur and recovery takes place on discontinuation of the drug. It is more effective in the adults than the antifolics.

Burchenal et al (1953)<sup>5</sup> treated 107 patients with 6-mercaptopurine (50 mg tablets at 2.5 mg/kg daily). Leukaemic patients improved without ill-effects while other patients with neoplastic disease showed toxicity without favourable clinical response. Children tolerate this drug better; 15 out of 45 children had haematological remission after 2-9 weeks, lasting 2 to 22 weeks. Of these, 5 out of 15, were amethopterin failures. 4 out of 18 adults with acute leukaemia had slight improvement, while 5 out of 9 adults with chronic leukaemia had temporary remission.

Burchenal et al (1954)<sup>4</sup> treated 269 patients having neoplastic diseases (140 with acute leukaemia, 8 subacute, 18 chronic myelocytic and 4 chronic lymphatic leukaemia). Children were given 6-mercaptopurine, 2.5 mg/kg orally, as a single daily dose and at this level very few toxic manifestations were seen. Antileukaemic effect became evident in 3-9 weeks of continuous therapy. It was not useful in chronic lymphocytic leukaemia, lymphosarcoma, Hodgkin's disease or metastatic carcinoma. Children with acute leukaemia showed a high percentage of remissions. Adults occasionally showed remissions but the results were not satisfactory. In early chronic lymphocytic leukaemia favourable remissions were obtained ; however, therapy needs to be maintained. Short remissions were seen in terminal acute stage of chronic myelocytic leukaemia.

**Adrenal Hormones :** Cortisone, hydrocortisone, prednisone and ACTH are sometimes effective in the control of acute leukaemia. While acute lymphocytic variety responds readily, acute granulocytic leukaemia may also respond. Bone marrow depression being minimal, these are the easiest of any of the agents to administer. Initial doses are larger. Three hundred to four hundred mg of cortisone, 60-80 mg of prednisone or 200 mg of ACTH daily may be well tolerated. Correspondingly smaller doses are used for children. Sodium chloride intake is reduced and potassium chloride is added to the diet. If benefit occurs, dosage may be maintained on quarter of the dose. Steroids reduce the intensity of haemolysis. Antimetabolites are contra-indicated in pregnancy while steroids are not.

In a report to the Medical Research Council of Great Britain (1955)<sup>13</sup>, a panel of haematologists studying 49 children and 52 adults with acute leukaemia, and 4 with chronic leukaemia, stated that ACTH and cortisone administration in the acute leukaemias may offer the most favourable means of inducing a remission, but the duration of prolongation of life is meagre.

**Myleran** may be useful in acute (usually terminal) phase of chronic granulocytic leukaemia and in acute granulocytic leukaemia.

**Nitrogen mustard** and related compounds, triethylene melamine (TEM) or triethylene thiophosphoramidate (Thio-TEPA) have no place in the treatment of acute leukaemia.

Beattie and Howells (1954)<sup>1</sup> treated 51 patients who did not have any radiotherapy ; cases of acute and chronic leukaemia and polycythaemia did not improve with nitrogen mustard therapy.

Smith et al (1955)<sup>15</sup>, treated 21 patients under 15 years (12 cases of acute leukaemia) with Thio-TEPA in saline (10 mg/ml) i.m. or i.v. in daily doses of 2-10 mg and concluded that the drug might be contraindicated in acute leukaemias. Toxic bone marrow depression implies caution.

Mills and Stickney (1956)<sup>12</sup> state that about 50 per cent of children and 35 per cent of adults with acute leukaemia will have clinical and haematological remission with antifolics or the hormones. The duration of remission is longer with the use of antifolics. Remissions lasting 3-15 months have been reported. In adults the incidence of remissions is not high and they do not last long enough. This is probably because adults usually suffer more from acute granulocytic and monocytic leukaemias, both of which are more resistant than the lymphocytic form.

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In acute leukaemia, the antimetabolites (amethopterin and mercaptopurine) should be the drugs of choice with cortisone and ACTH being reserved for emergencies, when the disease has become resistant to the antimetabolites, or when there is not sufficient time for the use of slower acting drugs (Burchenal et al, 1954)<sup>4</sup>.

Combined therapy holds much promise. Such has also been effective to a lesser degree in adults having acute or subacute leukaemias (Best and Limarzi, 1955)<sup>2</sup>.

	Acute and sub- acute leukaemia	Chronic granulo- cytic leukaemia	Chronic lympho- cytic leukaemia
Local X-ray .. .. .	0	++ ++	++ ++
P <sup>32</sup> Spray X-ray .. .. .	0	++ ++	++ ++
Nitrogen mustard .. .. .	0	+	++
TEM .. .. .	0	+	++
Urethane .. .. .	0	++ ++	+
Myleran .. .. .	0	++ ++	0
6-Mercaptopurine .. .. .	++ ++	+	0
Corticotrophin or cortisone .. .. .	++ ++	0	++

Comparison of results with various therapeutic agents in adults.

[From Best and Limarzi (1955)<sup>2</sup>].

**Chronic Leukaemia :** Chronic myelocytic leukaemia or chronic monocytic leukaemia may be treated with X-ray, radiophosphorus, urethane, nitrogen mustard, 6-mercaptopurine, TEPA or Thio-TEPA and myleran. X-ray therapy and myleran therapy have resulted in more satisfactory remissions and in general are least hazardous (Watkins, 1956)<sup>17</sup>.

Nitrogen mustards inactivate cellular enzymes and are nucleotoxic, acting directly on chromosomes. Chronic myelocytic leukaemia responds well.

TEM acts like nitrogen mustard. It may be given orally or i.v., but usually orally. Immediate toxic reactions are less. Its chief value is in the treatment of chronic lymphocytic leukaemia and is less effective in chronic myelocytic leukaemia. Severe bone marrow depression emphasizes close supervision.

TEPA and Thio-TEPA may be given orally, i.m., or i.v. (5-10 mg). Their action is similar to nitrogen mustard or TEM. There are fewer side effects and less toxicity. They are less effective and large doses are required.

Zarafonctis et al (1955)<sup>19</sup> treated nine cases of chronic granulocytic leukaemia and two cases of chronic lymphocytic leukaemia, with Thio-TEPA for periods of upto 20 months, at intervals. Bone marrow function is depressed. It may be used as a suppressive when given in properly regulated doses for long periods. Laboratory control is very essential.

Myleran has specific effect on granulopoiesis. It is useful in chronic myelocytic leukaemia, but not in lymphocytic leukaemia. It is given orally in 4 mg/day dose till the white cell count falls to 10,000 cells/c.mm. Platelet count reduction is an early sign of toxicity. Remissions of six to twelve months are often induced.

Bollag (1953)<sup>3</sup> treated 12 leukaemic patients with myleran, 4 mg/day for three to four weeks with clinical improvement. No side effects were noticed.

X-ray therapy is still a standard treatment for chronic granulocytic and chronic lymphocytic leukaemias. Radiophosphorus, urethane and myleran have proved quite effective in many chronic granulocytic leukaemias. P<sup>32</sup>, nitrogen mustards and TEM are useful in chronic lymphocytic leukaemia.

**Hodgkin's Disease:** Nitrogen mustards are chiefly used in Hodgkin's disease. However, they do not very much differentiate between the normal haemopoietic and the abnormal malignant tissue, so much so that there is sometimes severe bone marrow depression. Nitrogen mustards produce rapid fall in temperature and regression of the tumours. The remissions may last a few months to few years. They are the most effective if given in the first instance

but less useful if given to X-ray failure cases. X-ray and nitrogen mustard combination does not significantly improve the survival time (Mann, 1956)<sup>11</sup>.

Beattie and Howells (1954)<sup>1</sup> treated 27 patients with Hodgkin's disease ; only six survived. Initial response was favourable in some of the other cases.

Nitrogen mustard is given intravenously in saline drip (to avoid irritation and phlebitis). Four to five injections of 0.1 mg/kg are given on alternate days. Nausea and vomiting may ensue. Six weeks should elapse before the next course. The drug should not follow immediately after extensive radiotherapy.

McCarthy (1955)<sup>10</sup> used combination of corticosteroid and nitrogen mustard in 100 hospitalised patients. Nitrogen mustard was given for five days ; the average daily dose was 0.1 mg/kg body weight. ACTH was given 60-80 units, i.m./6 hourly, until last day; and cortisone was given 50-75 mg 4 hourly ; total dose was 300-450 mg, maintenance dose of 100-200 mg being continued orally. Three out of four patients with Hodgkin's disease survived for periods varying from 20 months to 3 years. ACTH and cortisone successfully abolished or reduced severe nausea, vomiting and bone marrow depression usually caused by nitrogen mustard. Complications and side effects are few and transient.

TEM is less effective but its oral administration is an advantage over nitrogen mustard. The adult dose is 2.5 mg with 30 gr of sodium bicarbonate given on empty stomach. It is given on alternate days, until 15 mg are given. It causes less of vomiting.

Actinomycin C is an antibiotic with some action is Hodgkin's disease but is less effective than nitrogen mustard. It is given in daily dose of 200  $\mu$ g rising gradually to 600  $\mu$ g until a total of 5000—10,000  $\mu$ g has been given. Toxic effects are thrombocytopenia and stomatitis.

**Polycythaemia :** This disease is characterised by an increase in the blood volume, circulating red cells and blood viscosity. The many distressing symptoms are due to haemodynamic imbalance. Treatment of this disease with radiophosphorus is now the accepted method. Patients are given dextran-replacement transfusion with simultaneous venesection, followed by i.v., injection of  $P^{32}$ . The entire treatment can be completed in two to three days. Subsequent injections of  $P^{32}$  are given as required (Mackay, 1957)<sup>9</sup>.

In polycythaemia the marrow is hyperactive, has an active phosphate metabolism, is sensitive to radio-action and lies close to the bone in which the phosphate is concentrated. When  $P^{32}$  is given, the abnormal degree of marrow activity can be reduced without irradiating the whole body.

Venesection, X-ray,  $P^{32}$ , and TEM have proved to be of value in polycythaemia (Best and Limarzi, 1955)<sup>2</sup>.

At first successive withdrawals of blood were made (500 c.cm at a time) to reduce haematocrit reading to 55 per cent or less. After this the patient is given i.v. radiophosphorus (5.7 to 8.3 millicuries mean dose). If there is no control, the course is repeated after 12 weeks. Of 142 patients studied more than 50 per cent were objectively controlled for over a year. Symptoms were relieved and dangers of thrombosis and haemorrhage were reduced (Stroebel and Law, 1956)<sup>16</sup>.

Isaacs (1954)<sup>7</sup> reported Daraprim to be useful in this condition. In experimental animals it caused aminopterin-like reactions, with lowering of the red and white cells. The dose is 25 mg once daily after breakfast until the red cell count approached normal and then maintained indefinitely on 12.5 mg daily. No toxicity was noticed.

**Thyroid Cancer :** By virtue of selective concentration of iodine in the thyroid, radio-iodine was expected to be useful in thyroid cancer, but this has not been completely realised. Only the more differentiated growths show worthwhile concentration of  $I^{131}$  and then always to a smaller degree than normally functioning thyroid tissue. Hence as much of the normal tissue is removed either by surgical procedures or by large ablation dose of  $I^{131}$ ; two to three months later, the uptake of small tracer dose of  $I^{131}$  is determined followed by therapeutic dose (100-150 m.c.) and this procedure is repeated at two to six months' intervals. The uptake of  $I^{131}$  by the malignant tissue may be increased by depression of normal tissue with antithyroid drugs for two weeks before giving the therapeutic dose of  $I^{131}$ ; conversely iodine administration is contraindicated in such patients (Mackay, 1957)<sup>9</sup>.

**Cancer of the Breast and Prostate:** The mechanism by which hormones induce or inhibit cancer is still obscure. The concept of 'hormone-dependent' and 'hormone-independent' has cur-

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rently come into use. In many cases, prostatic cancer is inhibited by 'anti-androgenic' therapy, in the form of castration and oestrogen therapy; in others cellular proliferation is unaffected. In the same way carcinoma of the prostate and the breast are responsive to adrenalectomy or hypophysectomy, while others are resistant. The effects of adrenalectomy are presumably due to elimination of the sex hormones. Tumours continue to regress after adrenalectomy even though they are maintained on cortisone. The effects of sex hormones on cancer of the breast are paradoxical. Oestrogens are carcinogenic, at least in animals. Women in whom menopause occurs late are more prone to develop carcinoma, possibly as a result of longer duration of oestrogenic activity. The biological effects of oestrogens are proliferative rather than inhibitory. Yet oestrogen therapy is of benefit in advanced cancer of the breast of postmenopausal women, whereas before menopause androgenic therapy is most effective. This has suggested that the therapeutic action of sex hormones may be to alter the internal environment (Editor, B.M.J. 1956)<sup>6</sup>.

Pearson and Lipsett (1956)<sup>14</sup> present the results of various workers in endocrine treatment for metastatic breast cancer in the following table.

Treatment	Status	Number of cases	Objective remissions (per cent)	Duration (Months)	
				Mean	Median
Oophorectomy .. .. .	Premenopausal ..	75	44	9	6.5
	Postmenopausal ..	21	10	..	..
Adrenalectomy .. .. .	(All previously oophorectomized)	38	45	9	7
Combined oophorectomy and adrenalectomy	Postmenopausal ..	25	64	9 1	..
*Hypophysectomy .. .. .	All ages .. ..	41	51	..	..
Androgen (testosterone propionate 100 mg, three times a week).	All ages .. ..	416	23	7.5	4.5
Estrogen (stilboestrol 15 mg/day or Estinyl 3 mg/day).	Postmenopausal (5 1 years).	381	44	8	4.5
Cortisone--					
200-400 mg/day .. .. .	All ages .. ..	39	31	3	3
50-75 mg/day .. .. .	All ages .. ..	14	14	2	..

\*Preliminary observations from a group of 58 patients in whom the results of hypophysectomy could be evaluated. Results of endocrine treatment for metastatic breast cancer.

From Pearson & Lipsett (1956)<sup>14</sup>.

Lewison et al (1957)<sup>8</sup> treated 133 patients receiving 223 complete courses of treatment with sex hormone therapy for advanced mammary cancer. The choice between estrogen and androgen was made principally on the physiological age of the patient in reference to her menopause. Oestrogens were used only five years after the menopause while androgens were found to be useful both in premenopausal and postmenopausal patients. Very old people responded to oestrogens.

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## MALIGNANT EPITHELIAL TUMOURS OF THE LUNG

D. Jaganatha Reddy

Wide publicity is given to the alarmingly increasing incidence of bronchogenic carcinoma of the lung in recent years, both in medical publications and in lay journals. That this increase in the incidence of malignant epithelial cell tumours of the lung is real and not apparent is confirmed by the reports of Graham and Wynder from America and Hill and Doll from Great Britain. These authors have pooled data to substantiate the fact that the incidence is more in urban areas and in people who volunteered history of heavy cigarette-smoking for periods of 20 or more years. The observations have raised the question of the presence of a carcinogen substance in tobacco. This disease is seen in people above 50 years of age, preponderantly in the male sex. The sex incidence of this neoplasm varies from 1 in 10 to 1 in 20. It does not mean that in the female sex there is some sort of protection against pulmonary carcinoma, since Greene's transplantation experiments of small fragments of the growth into the cornea of male and female mice conclusively proved the absence of specific factors related to the sex and interfering in some way with the growth of the transplant—they grew well in both the groups of mice. The low incidence of bronchogenic carcinoma in the female is attributable to the relatively fewer members of the sex being used to smoking. Girls and young women have taken to smoking in the postwar period and sufficient time has not elapsed for them to develop the tumour and pathologists forecast an increase in the incidence of pulmonary carcinoma in women in Great Britain and America in the coming two decades. There has been a tremendous increase in the consumption of tobacco in the Western countries and this parallels the increase in lung carcinoma. Very interesting observations have been made by Dungel of Iceland who attributes the low incidence of bronchogenic carcinoma in the population of Iceland to low *per capita* consumption of tobacco and apprehends that 20 years hence a rise in the incidence of the same because of the increase in use of tobacco during the post-war period.

All surveys point out that 95 per cent of patients of carcinoma of the lung are heavy smokers. Arsenic, special blends of tobacco, etc. do not appear to possess carcinogenic properties ; many authors recognise or suggest liberation of a potent carcinogen at the time of combustion of cigarette. It is believed that the heat elaborated during cigarette combustion is enormous. Several workers have induced cutaneous cancer in mice by painting the skin with condensed cigarette smoke. They have also drawn attention to the lag period that elapses between the appearance of cancer after the cessation of painting. This is further substantiated by development of bronchogenic carcinoma in Schneeberg mine workers long after their discontinuance of work in the mines.

Early diagnosis of bronchogenic carcinoma is not usually made because the condition is often mistaken for inflammatory conditions, abscess, bronchiectasis, etc. and very often these cases prove fatal, from 8 months to one year after the diagnosis is made. With the improvement in Roentgen and biopsy methods, cytological techniques, thoracotomy, etc., more cases are being recognised in the early stages. Mass radiography in tuberculosis survey is disclosing occult, peripherally placed and asymptomatic carcinoma of the lung ; lobectomy and pneumonectomy when indicated have saved the lives of many patients.

## Malignant Epithelial Tumours of the Lung

These tumours arise from the main bronchi and very often occlude the lumen and lead to collapse, abscess or bronchiectasis. The tumour may remain small or involve the entire lung. In a large series of cases nearly 60 per cent of them were of epidermoid type and these are by far encountered more often in the male sex and invariably associated with a positive history of smoking. This type is infrequently met with in women. Adenocarcinoma accounts for 10 to 15 per cent of the cases and is seen more often in women. Both these types presage favourable prognosis. Anaplastic carcinoma, either the small or the large-cell variant, occurs in 25 to 30 per cent of cases and is again most frequently seen in the male. The prognosis for this histological type of pulmonary carcinoma is most gloomy.

Yet another epithelial tumour of the lung has attracted the attention of the clinician and the pathologist in recent years. This is the alveolar-cell carcinoma or pulmonary adenomatosis. This tumour is said to occur in the benign and malignant forms. It may be seen in diffuse form, simulating both clinically and on gross examination lobar pneumonia in the grey hepatisation stage, or in the nodular form. The disease is not recognised until in the late stages and so is invariably fatal. The clinical picture is indistinguishable from acute or chronic pulmonary infections. Histologically it is composed of columnar-cell tumour with or without the ciliary lining of the mucus-containing alveoli. It is supposed to arise either from the alveolar epithelium or from the terminal bronchioles. The aetiology is the subject of continued controversy. At one time it was believed to be of viral origin because of its resemblance to the epizootic Zaagsiekte disease of sheep but now it has been thought of as neoplastic in nature. Tobacco smoking appears to have no causal relationship and its incidence in the two sexes is practically equal.

The incidence of bronchogenic carcinoma of the lung in India is not yet reliably known. Reports from different parts of the country appear to indicate varying incidence. Viswanath and Grewal from the North, Gharpure from Bombay and Reddy and Reddy from South India observed negligible incidence of this neoplasm. Reddy and Reddy found only one necropsy report of bronchogenic carcinoma in 1650 necropsies registered at the Andhra Medical College and this almost compares to the low incidence observed by Strachan in Johannesburg in South Africa. But the authors caution that the necropsy incidence need not reflect the real occurrence of the condition for many cases may have been clinically missed. Basu from Calcutta reported 37 surgically treated cases and they were exclusively in the male sex. He correctly stressed the need to use skiagraphy including tomography, bronchography and angiography in the early detection of the condition. He also recommends exploratory thoracotomy for establishing the diagnosis. The histological diagnosis in this series is as follows :

Squamous cell carcinoma	..	..	..	..	..	..	..	14
Anaplastic carcinoma	..	..	..	..	..	..	..	10
Adenocarcinoma	..	..	..	..	..	..	..	4
Undetermined	..	..	..	..	..	..	..	11

Radical pneumonectomy is commended by Basu and he stresses the use of radiology in the diagnosis of peripherally located bronchogenic carcinoma which very often pursues a silent course.

Dutta Choudhari recently laid stress on the importance of cytological diagnosis of carcinoma of the lung and Roy reported on the role of Roentgen therapy for patients suffering from bronchogenic carcinoma.

Most instructive and painstaking report of bronchogenic carcinoma of the lung is by Banker. He has vehemently disputed the observations of Hill and Doll in that the incidence of carcinoma of lung is not low in India. He further brought forward evidence to show that the original report of Gharpure did not include cancer of the lung at all on which were based the conclusions of Hill and Doll and that Gharpure in a separate paper for the same period found 21 out of 22 chest carcinoma to be primary tumours of the lung. Statistics from the Indian Central Tobacco Committee show that there has been an appreciable increase in the consumption of cigarettes and *bidis* during the period 1948—1953, throughout India. Banker reviews clinicopathological findings in 43 necropsies of bronchogenic carcinoma registered at the K.E.M. Hospital, Bombay. He feels that as the average age at which death takes place in India greater number of cases of bronchogenic carcinoma are bound to occur. 88.4 per cent of the series were males. Very interesting is the finding that only three cases in the series were of epidermoid carcinoma while 28 were of anaplastic and 12 of adenocarcinomatous type. He hints that this strange

findings in histology of the bronchogenic carcinoma in his series may suggest yet another aetiological agent quite distinct from tobacco carcinoma.

Andrews and Monteiro reported a case of alveolar-cell carcinoma confirmed at necropsy. The condition was missed clinically and also at autopsy where it was mistaken for lobar pneumonia. Microscopic study revealed the true nature of the neoplasm. There were no secondaries and no other primary growth was spotted at autopsy.

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**MEDICOLEGAL ASPECTS**—See BLOOD GROUPS, BLOOD STAINS, ALCOHOL POISONING, MEDICOLEGAL ASPECTS OF

### MENINGITIS, TREATMENT OF

C. V. Talwalkar

Meningitis has no longer remained the dreadful disease that it once was—thanks to the present antibiotic age. One can almost guarantee a success in the majority of cases, where treatment is started early during the course of the disease. Only in those cases admitted in a moribund state, the outcome is doubtful but even many of them have been saved with energetic treatment. Tuberculous meningitis which was for many years an invariably fatal disease has been brought within the possibility of cure by early diagnosis and prompt chemotherapy.<sup>16</sup>

The main drugs found useful in the treatment of meningitis are—sulphonamides, penicillin, chloramphenicol, streptomycin, isoniazid and p-amino salicylic acid. Other wide spectrum antibiotics like Terramycin, Aureomycin, Achromycin, etc., have occasionally been used when the organisms have developed resistance to the former group, but on the whole, their use has not been so extensive. Polymixin B has been used particularly in infections with *B. pyocyaneus*<sup>4,32</sup>. Recently there is a greater tendency to use cortisone or ACTH particularly, in tuberculous meningitis<sup>14,20,3</sup> to control the toxæmia and prevent fibrosis and intraspinal obstruction.

The routes of administration are—oral, intramuscular, intravenous or intrathecal. On many occasions a combination of two or more routes is desirable. The intrathecal route has been the subject of controversy for the last 4 or 5 years but with the passage of time, advocates of this route have been losing ground, of course with immense relief to the victims of tuberculous meningitis. Hoyne<sup>9</sup> believes that once the diagnosis of meningitis is established by lumbar puncture, most of the patients can be cured with appropriate chemotherapeutic or antibiotic agents if treatment is started early in the course of the disease. The initial dose is given intravenously followed by either intramuscular or oral therapy. According to him, it is not necessary to introduce the therapeutic agent in close contact with infected tissues, and spinal puncture, although relatively a safe procedure, is occasionally attended by unpleasant sequelae or even serious complications. Hoyne<sup>10</sup> has listed about a dozen objections to intrathecal therapy. On the other hand, Lorber<sup>18</sup> still advocates a minimum of seven weeks of intrathecal therapy as the treatment of choice for tuberculous meningitis.

**Meningococcal Meningitis:** Sulphonamides<sup>25</sup> are usually effective. Penicillin is not always required, but if at the time of carrying out a lumbar puncture, the cerebrospinal fluid is obviously turbid 10,000 to 20,000 units are injected intrathecally and if the laboratory report shows the



## Meningitis, Treatment of

presence of meningococci further penicillin is not administered. Stanley Banks<sup>30</sup> states that meningococci still do not show any significant resistance to the more powerful sulphonamides and for ordinary form of the disease no adjuvant drug is usually required. Sulphonamides have also been used in mass chemoprophylaxis of meningococcal disease during the Second World War<sup>1</sup>. Treatment was given in a single dose of 2.5 g orally to the whole of the group or population concerned and it reduced the carrier rate for at least three weeks and substantially reduced or put an end to clinical cases within the group. The dosage of sulphonamide for a clinical attack should be fairly high. No infant<sup>30</sup> should receive less than 3 g daily for three to four days, and for adults<sup>22</sup> at least 9 g daily should be given for the same length of time. The total course should last for 5-7 days. In this form of meningitis<sup>2</sup> sulphadiazine has remained the drug of choice for more than 15 years. By *in vitro* studies, Love and Finland have demonstrated that of the 50 different strains of meningococci tested, all except six were completely inhibited by sulphadiazine in a concentration of 50mg/c.cm (5 mg/100 c.cm) or less which is well below the highest level of sulphonamide that can readily be maintained in the blood and cerebrospinal fluid on oral therapy. Choice of the sulphonamide is an individual factor. Sulphadiazine has been a popular choice for several years but in Hoyne's experience<sup>10</sup> it has caused haematuria far more frequently than any of the other sulpha drugs. He used sulphathiazole in several hundred cases with exceptionally good results and in spite of the warning given with the drug "Do not use for meningitis". Sulphamerazine and sulphasoxazole (Gantrisin) are claimed to be the least toxic. It is a routine procedure to administer the initial dose of the drug intravenously as a 5 per cent solution of the sodium salt in a pint of 5-10 per cent dextrose by a slow drip infusion. If the patient is still comatose at the end of this drip a second dose is repeated, otherwise the drug is given intramuscularly, in two doses at 12-hour interval. If the patient is conscious and can swallow, the drug is given orally. In case of severe shock and collapse associated with Waterhouse-Friderichsen syndrome, cortisone or hydrocortisone is used as described later in the therapy of tuberculous meningitis; intravenous drip of 5 per cent glucose containing 4 mg of noradrenaline per 1000 c.cm may be life saving.

*Pneumococcal Meningitis*: Penicillin is the antibiotic of choice in this infection. There is again a difference of opinion as regards the necessity of intrathecal injection. Various authors like Pengelly<sup>23</sup>, Stanley Banks<sup>30</sup>, McKenderic<sup>19</sup> and Paterson<sup>22</sup> insist upon a daily intrathecal dose of 20,000 units for 7-10 days. On the other hand, other workers<sup>10,12,15</sup> prefer to give larger doses of penicillin intramuscularly, more frequently. Some workers have given sulphonamides in addition to penicillin<sup>23, 30, 19, 22</sup> while others have used a combination of penicillin and chloramphenicol<sup>12</sup>. A combination of penicillin and chlortetracycline (Aureomycin) has definitely worsened the prognosis<sup>30, 23</sup>. Hoyne<sup>10</sup> has used oxytetracycline (Terramycin) 500 mg intravenously by drip method in 5 per cent glucose as an initial dose and then 250 mg every four hours orally if the patient is able to swallow, otherwise parenterally for 6-8 days. The dose of penicillin should be very high, for instance<sup>12</sup>, one million units every two hours on the first day, then four hourly for 5-7 days, when there is no intrathecal medication, while with intrathecal dose of 20,000 units daily the intramuscular dose of 100,000 to 1,000,000 units is given in 24 hours at 3-4 hourly intervals<sup>23</sup> or 250,000 to 500,000 units four hourly for 4 or 5 days<sup>30</sup>. Pneumococcal meningitis is often a secondary complication, where the primary disease may lie in the middle ear, the lungs, the paranasal sinuses or due to skull defects<sup>19</sup>. Appropriate surgical treatment for the primary disease is given as soon as the patient recovers from meningitis. Talwalkar<sup>31</sup> has described a series of 20 cases of pneumococcal meningitis. Penicillin was used intrathecally in 10 cases with a 50 per cent survival rate, while there was not a single survivor in the remaining 10 cases. He attributes this high mortality to inadequate treatment either in the form of omission or insufficient dosage of sulpha drugs or delay in its use and omission of intrathecal penicillin. Hoyne<sup>10</sup> states that a low cell count in the cerebrospinal fluid with innumerable organisms is a bad omen.

*Haemophilus influenzae Meningitis*: Today the drug of choice for this infection is chloramphenicol by the oral route<sup>30</sup>. The spinal fluid becomes sterile in at least two thirds of the cases within 24 to 48 hours and in 100 per cent in 72 hours. Clinical recovery is correspondingly rapid and practically there are no complications or relapses and residual neurological damage is rare. Koch and Carson<sup>11</sup> have analysed 128 cases of *H. influenzae*, type B meningitis seen between 1930 to 1953 and have shown how complications have minimised and the mortality rate brought down since the introduction of antibiotics. In the earlier period, a 100 per cent mor-

tality was observed in a series of 14 patients receiving only supportive treatment whereas, there were two survivors in a series of 13 who were treated with sulphonamides alone; addition of Alexander's anti-rabbit serum caused only two deaths among 12 patients. In 1946 streptomycin was added to this regime and there were two deaths in a series of 27 patients. With the use of tetracycline in 1949, in addition to streptomycin and sulphonamide, there were again two deaths in a series of 46 patients. The authors have used chloramphenicol in their last series of 16 patients in various combinations with other drugs and there were no deaths. The dosage of chloramphenicol should be 200 mg/kg daily<sup>12</sup>, at 6 hour intervals. If the patient is comatose, initial dose of 100 mg/kg may be given intramuscularly. The duration of treatment is for 7-9 days. The drug is excreted freely in the cerebrospinal fluid and intrathecal medication is not required. It may be advantageously combined with a sulphonamide in the same dosage as for meningococcal infection. Both of these drugs are known to depress the bone marrow and frequent blood counts should be done to know the behaviour of the marrow. The drugs should not be used for more than a week to 10 days to minimize the risk of aplastic anaemia<sup>10</sup>. Majority of the cases respond much earlier and hence there is no real danger in using these drugs routinely.

*Pseudomonas pyocyaneus Meningitis*: This organism seems to be resistant to sulphonamides and the commoner antibiotics. It is known to be sensitive to polymixin B which is relatively a toxic drug. Ordinarily, the organism is of low virulence, but may produce clinical disease when introduced inadvertently into various areas of the body during certain procedures. Meningitis due to pseudomonas has followed simple lumbar puncture, injection of serum, unsterile solution of a spinal anaesthetic, antibiotics, etc. Trapnell<sup>32</sup> has described a case following a cerebrospinal fistula resulting post-operatively in a case of cervical ependymoblastoma. The organism was resistant to sulphonamides, penicillin, oxytetracycline, and chloramphenicol, but sensitive to polymixin B. Recovery followed a long course of intrathecal and intramuscular polymixin B. The dosage recommended<sup>30</sup> is 5 mg/kg daily, divided in 4 doses and one or two intrathecal doses of 4 mg each. Biehl and Hamburger<sup>4</sup> have described six cases of pyocyaneus meningitis. Penicillin, streptomycin and oxytetracycline were used in first two cases and were found of no use as both the patients died. In their third case the organisms were cultured from the C.S.F. very late in the course of the disease and polymixin was of no avail. This case illustrates the difficulty of isolating the organism, only one of the six fluid cultures having been positive. Polymixin B was definitely responsible for recovery in case Nos. 4 and 5 while case No. 6 might have responded both to polymixin and chloramphenicol. Trapnell<sup>32</sup> has recorded the following toxic effects: severe eosinophilia, xanthochromia in the C.S.F., nausea, malaise and pain at the site of injection, pain down the legs and back, transient mild albuminuria and cylindruria.

*Haemolytic Streptococcal and Staphylococcal Meningitis*: The treatment of these varieties is same as pneumococcal<sup>30</sup> but in cases of staphylococcal infection where the organism is resistant to penicillin, chloramphenicol and sulphadiazine should be used as described under *H. influenzae meningitis*. Some strains of *Streptococcus viridans* are relatively insensitive to penicillin and require very large doses. Smith and Davis<sup>28</sup> have described two cases of bacterial meningitis treated with Neopenil (diethylamino ethyl ester hydriodide of penicillin G). They describe that spinal fluid concentration was approximately ten times higher with Neopenil than with equal doses of penicillin G procaine, penicillin G potassium, or dibenzyl penicillin G. The implications of this have created a great deal of interest as it is known that penicillin administered parenterally does not readily diffuse across the thecal barrier, requiring intrathecal medication. Moll and Warmington<sup>20</sup> have treated 31 cases of purulent meningitis with Terramycin and sulphadiazine in dose schedule of 100 mg/kg of the former and 200 mg/kg of the latter drug daily for 10 days. There were only two deaths.

*Salmonella*<sup>19</sup> meningitis seems to respond to chloramphenicol but according to Broom<sup>5</sup>, in leptospiral meningitis though Aureomycin and Terramycin appear to be the preparations of choice, drug therapy in general is very disappointing.

*Tuberculous Meningitis*: Bulkeley<sup>6</sup> has adopted the following regime as a standard treatment for this infection. He gives streptomycin i.m. with oral isoniazid and p-amino-salicylic acid together with ACTH to prevent arteritis and the formation of organizing exudates. Fitzpatrick<sup>13</sup> used oral INH and PAS and streptomycin by i.m. route only and the fluid became

## Meningitis, Treatment of

normal after an average of 6.1 months. The Veterans Administration Study<sup>13</sup> in the U.S.A. has shown in a large series of 287 cases that in a group of 39 cases who received INH in combination the survival rate was highest. The conclusion that intrathecal streptomycin may no longer be necessary seems to be justified. Smellie<sup>27</sup> treated 15 children on streptomycin i.m. (20 mg/lb body weight) daily for 4 months and then twice weekly for the fifth month and INH (4 mg/lb body weight) daily for 5 months or longer. There was only one death and one child was mentally and physically retarded, the remaining 13 cases showing eminently satisfactory results. INH given orally, readily and rapidly diffuses in the C.S.F.<sup>8</sup> and probably gains direct access to tubercle bacilli in the cells. The treatment in cases of tuberculous meningitis<sup>24</sup> should be for a minimum period of six months and it is preferable to continue in most cases for at least one year.

Lorber who is still in favour of intrathecal therapy has in an earlier report<sup>17</sup> divided his patients into two groups, one receiving INH (12 patients) and the other not receiving the drug (10 patients). Other treatment including streptomycin i.m. and intrathecal, and PAS, was identical for the two groups. Patients in the INH group required fewer intrathecal injections (average 65) compared with controls (average 90). He concludes that INH is a valuable addition to other drugs but it has not eliminated the need for intrathecal streptomycin treatment. In a later report<sup>18</sup> he has standardized the treatment which consists of INH 20 mg/kg daily for six months, streptomycin 40 mg/kg i.m. daily for six months and 25-50 mg intrathecally daily for six days and then thrice weekly for seven weeks—i.e., a total of 25 injections and PAS 0.5 g/kg daily for six months. Follow-up for an average period of 21 months showed that only one child out of 20 cases treated on this regime expired. It takes about 6-7 months for the fluid to return to normal, the proteins returning to normal a month or two earlier. The author has not used cortisone and in his experience spinal block is not common; he observed it in only one case out of 51 treated with INH. Lincoln and Sifontes<sup>16</sup> who have used intrathecal streptomycin mention the occurrence of block which is often the cause of failure of therapy in tuberculous meningitis. Smith and Vollum<sup>29</sup> have described the use of PPD (purified protein derivative) tuberculin intrathecally in the treatment of block and published results of several successful cases. Dubos<sup>7</sup> is of the opinion that intrathecal administration of tuberculin brings about an intense inflammatory reaction at the site of the lesion. The inflammatory cells bring to the lesion a supply of proteolytic enzymes which may exert some destructive action on the fibrin. Furthermore, it is possible that the allergic reactions bring about an activation of the normally inactive protease of the serum and that this enzyme can also attack fibrin. The proteolytic attack on fibrinous lesions brings about a release of bacilli into the spinal fluid or at least makes them more available for drug action.

Hitherto, efforts to combat local obstruction produced by tuberculous exudates have been restricted to the introduction of PPD tuberculin, heparin, streptokinase and even trypsin into the cerebrospinal fluid after obstruction has developed. Ashby and Grant<sup>3</sup> believe that such methods are hazardous and disappointing in their results. Cortisone is known to inhibit the formation of exudates. The authors describe 12 cases, six of whom had cortisone, the other treatment being same for the entire group. The cortisone group showed early clinical improvement, cell count in the C.S.F. went down very rapidly and the sugar level rose to normal very early. Of the controls, one died and three others had some neurological complications, while in the cortisone group all recovered without any complications. The editor of B.M.J.<sup>14</sup> in a leading article has warned that although there is no evidence up-to-date that cortisone given in this manner enhances the tuberculous infection, there are risks that pyogenic infections may supervene and that these might be difficult to recognise. On the other hand Shane and Reilly<sup>28</sup> who treated 7 cases on combined cortisone and antimicrobial agents found that resolution of established block occurred in one case, and in another development of incipient block was suppressed by cortisone. They conclude that the benefits from cortisone are due to suppression or reversal of the inflammatory process. It is highly probable that suppressive action is the prime factor in preventing the sealing off of the strategic foramina at the base of the brain which frequently result in irreversible hydrocephalus. In their experience pulmonary lesions were not made worse by the treatment. They have used cortisone orally 200-300 mg daily until there was decided improvement in the clinical and laboratory findings. Montgomery, Benedek and Poske<sup>21</sup> conclude that the cortical hormones should be administered briefly in severely toxic patients to give the chemotherapy time to take effect.

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MIDDLE EAR, GLOMUS JUGULARE TUMOURS OF

J. V. DeSa

These tumours occur along the tympanic branch of the glossopharyngeal and the auricular branch of the vagus nerve. More than 50 per cent of these tumours are in the adventitia of the dome of the jugular bulb.

The tumour is a non-chromaffin paraganglioma. It differs from other paragangliomas in that it contains little chromaffin tissue and is non-ephedrine producing. Sections show large irregularly-arranged eosinophils with hyperchromatic nuclei and numerous thin-walled vascular spaces—angioendothelioma. The tumour is benign, but locally invasive and thus lethal. Malignant degenerative changes causing distant metastases in organs such as the liver, lungs and the spine have been reported.

A recurring bloody polyp and X-ray showing erosion in a sclerosed mastoid are the diagnostic findings. Deafness, tinnitus, vertigo and facial paralysis may complicate the picture. Destruction of the petrous apex or invasion of the posterior nasopharynx indicate a very advanced growth, not amenable to surgery.

Treatment is either surgical excision or radiation therapy, the former being the one of choice. Use of androgens or oestrogens has been suggested since the incidence of these tumours is higher in the female sex. No results have been reported with such therapy.

Various techniques have been suggested for the surgical extirpation of the tumour. The technique of George Shambhaugh, Jr., merits particular attention.

## Mouth and Pharynx, Submucous Fibrosis of

The tympanic cavity is explored by an endaural incision, preserving the skin of the post-meatal wall. The anterior and inferior osseous wall is thinned down. The fibrous annulus tympanicus is elevated, the pars tensa folded on itself and the bony sulcus resected inferiorly exposing fully the hypotympanum and the tumour with it. With larger tumours radical mastoidectomy with exposure of the hypotympanum and, if necessary, the jugular bulb may prove useful.

If the tumour cannot be extirpated completely, the operated area should be subjected to deep X-ray therapy. Implantation of radon seeds has also been reported to have given good results.

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## MOUTH AND PHARYNX, SUBMUCOUS FIBROSIS OF T. B. Gupta and M. Mohsin

Cases of submucous fibrosis of oropharynx have been noticed by the writers only during the last 8 to 10 years. During this very period reports of such cases in different parts of India have appeared from time to time in the literature. The disease has not been reported from any other country and considering the absence of any mention of this condition in the various text-books, it would be clear that in our country also, its incidence has been more reported since a decade or so. Literature on this subject is extremely meagre. Apart from the few articles which have been duly acknowledged, the writers have had to draw upon their own observations and experience. During this period, about 50 cases came under our observation.

The condition as we find, appears to be a localised disorder of the connective tissue of the mucosa of the oral cavity, affecting the palatal, faucial, and the buccal muscles in advanced cases and is characterized by the formation of fibrous bands resulting in progressive inability to open the mouth properly. It is possibly a type of collagen disease, in which there is fibrinoid degeneration of collagen tissue which can be regarded as the basis of pathological change.

Geographical distribution: In India, so far, cases have been reported from Nepal, Bihar, Bombay, Madras and Hyderabad. A few cases have been also reported from the Punjab and Assam.

**Aetiology:** There is no known aetiological factor. Various suggestions have been made. The habit of chewing betel nuts has been found in the majority of patients. Some observers have laid stress upon the quantity as well as the variety of the nut consumed by such patients. Majority of them were habituated to take 15 to 20 nuts per day. We do not however, consider this habit to have anything to do with the aetiology of this disease, firstly, because as we know, this habit is prevalent amongst our people for centuries and the disease has not been reported till during the last few years. Secondly, the disease has not affected those who are known to be taking large quantities of nuts all their lives. Further work in this direction might settle the point. At present we think the aetiology to be obscure.

No age is exempt, as cases have been found in children of 8 to 10 years and in old persons of 60 years or more, but the commonest age incidence is between 12 and 35 years. Males have been found affected almost twice as often as females and all social groups have equal share. Syphilis, lupus, diphtheria and scarlet fever do not seem to have any aetiological influence in this type of fibrosis. Helminthic infection and vitamin B deficiency do not have any significant role in its aetiology.

Lalchand (1950) records cases from Nepal associated with the habit of taking unfiltered river water.

**Pathology:** Inspection of the oral cavity presents a white appearance of the mucous membrane of the hard and the soft palate instead of the normal pink colour. Anterior and posterior pillars appear like white fibrous bands and are generally greatly shortened (which is responsible for the inability to open the mouth properly). In some of the cases, epithelial erosion and sub-epithelial haemorrhages are seen. In advanced cases, white fibrous tissue traverses the substance

of the tonsils which are pale, adherent and fibrosed. In certain percentage of cases fibrous change also takes place in the mucosa of the cheek which is thickened, inelastic and firm in consistency.

Thus according to the distribution of fibrous tissue, 3 varieties can be recognised:

1. Palatal—in which the soft palate is only involved.
2. Faucial—in this, in addition to the soft palate the anterior and the posterior pillars are affected.
3. Buccal—mucosa of the cheeks is affected.

Histologically there is acanthosis of the epithelium which is of the stratified squamous type (at places there is definite atrophy and at other places there is hypertrophy particularly of the middle layer). Thin-walled blood vessels and occasionally mucous glands are seen beneath the epithelium. The sub-epithelial layer is mostly occupied by hyalinised collagen tissue and at places, changes are suggestive of fibrinoid degeneration. Deep to the hyaline tissue, striped muscle fibres are seen, some of the bundles of the muscle fibres undergoing necrosis and degeneration. There is patchy leucocytic infiltration in some of the cases.

*Symptoms:* The onset is in all cases insidious. Joshi classified the cases into two categories according to the presenting signs and symptoms:

1. Asymptomatic—The condition in this group is detected in routine examinations accidentally, the patient not having noticed any of the difficulties associated with this disease.

2. Symptomatic—In this group of cases the symptoms may date from an attack of fever or pharyngitis which the patient usually forgets. Glossitis is present and burning sensation is experienced on eating spicy food, so that the patient restricts himself to bland diet. Protrusion of the tongue is restricted and pain is felt at the junction of the pillars and the tongue while opening the mouth. There is increasing difficulty in opening the mouth which in extreme cases may lead to lock-jaw. The jaws cannot be separated more than 5 mm. Solid food cannot be taken, even pasty stuff is taken with difficulty.

The examination of the mouth in advanced cases is a matter of great difficulty. The colour of the mucous membrane is white instead of pink. The uvula stands out prominently pink in contrast to the white colour of the palate, fauces and the buccal mucosa. Occasionally, a few spots of sub-epithelial round-shaped haemorrhages are seen in the mucosa. No gross pathology is observed beyond the posterior pillars. The larynx is usually normal, but in advanced cases, similar appearances have been traced down to the level of the pyriform fossa (Rao and Raju). The tonsillar and the cervical lymph glands are not enlarged and the temporomandibular joint is free.

In the early stage of the disease, vesicles indistinguishable from vesicles of herpes, are seen on the palate and pillars. These vesicles rupture giving rise to superficial ulcerations (epithelial erosions) and stomatitis. It has been noted that the distribution of ulceration and stomatitis is not like that associated with vitamin B deficiency. The ulcers may be oval, round, or kidney shaped and are surrounded by a faint red areola.

We are of the opinion that a thorough investigation of each case on the following lines should be carried out, in as much as, the real aetiology is still shrouded in mystery, having baffled all attempts of different workers in different places.

- (a) Gastric analysis
- (b) Total and differential blood counts
- (c) W. R.
- (d) Stool examination
- (e) Evidences of any deficiency disease
- (f) Vitamin C content of blood
- (g) Estimation of blood proteins
- (h) Culture from the vesicle in the early stage
- (i) Biopsy

*Diagnosis:* This is usually easy from the characteristic clinical features. Besides the ordinary histological findings, there is present hyperglobulinaemia and electron microscopy can be of help in these cases.

*Treatment:* There is no satisfactory treatment. In planning to treat such a case, it has to be remembered that in the normal process of opening the mouth, once the condyles of the mandible

## Myasthenia Gravis

have slipped into the glenoid fossae, the elasticity of the tissues comprising the mucous lining of the oral cavity plays an important part besides the contraction of the muscles concerned. With the fibrous change in the mucosa, not only the elasticity of the tissues is lost, but the thick fibrous bands act as check ligaments interfering in the opening of the mouth. To restore the proper opening of the mouth, the elasticity of the mucous lining of the oral cavity has to be regained. Various medical and surgical procedures have been advocated.

(a) Orally, a course of cortisone tablets has been given for 2 to 3 weeks (Rao and Raju) upto a total dose of 2,000 mg. Gradual vascularisation appears from the periphery. The fibrous tissue has been reported to become soft and elastic and allowing the lower jaw freer movement. Encouraging reports have appeared as a result of this therapy.

(b) Local infiltration of dihydrocortisone into the fibrous tissue has also been tried. The suspension is infiltrated into the fibrous tissue. The site of infiltration is changed every time. The process has been continued for weeks till softening of the fibrous tissue takes place and the mouth gradually begins to open. The disadvantage of this therapy is the danger of relapse after discontinuance of the drug. Local infiltration, however, gives better result and there is no untoward side effect.

Local injections of cortisone could also be tried. This could be given in the form of fine suspension in aqueous media containing little benzoic acid as preservative. Suspension of 25 mg per ml, 1/4 to 1/2 ml to start with, and in increasing amounts every alternate day can be injected into the submucosa. Depot effect can be obtained analogous to that by implantation of hormone tablets. During the course of treatment with cortisone, the body weight should be checked up at intervals and any evidence of salt retention (sodium) as for example, oedema of face should be noted promptly. The treatment in such circumstances should be stopped for some time. It has been observed that early cases do well with cortisone therapy—local or systemic. Cases have been observed in which there has been no recurrence up to a period of 2 years. In case of recurrence, cortisone can be resumed with maintenance dose of 20 mg per day for a few weeks.

The fibrous bands of anterior and posterior pillars and in the mucosa of the cheeks might be cut deep to the muscles with advantage by electric cautery or diathermy knife, under local anaesthesia, and the mouth could be opened gradually, first with a tongue depressor. Once the mouth is opened, the mobility of the jaw can be maintained by active movements and the wound can be allowed to heal. When the jaw separates sufficiently to allow the application of a mouth gag, the patient can be put under general anaesthesia, for cutting the fibrous bands and opening the mouth fully. We are of the opinion that the fibrous tissues should be surgically dealt with gradually in 4 or 5 sittings at intervals of 10 days or so. At first only the anterior pillars should be tackled. This procedure has given very good results particularly in palatal and faucial types of cases. The jaws separate adequately and the tongue can be protruded normally. The interdental interval between the lower and the upper incisors after treatment has become in many cases about 1 inch. If this amount of separation of the jaws is maintained for a period of 3 months, it is likely to remain so thereafter. We have followed cases after this treatment up to 2 years without relapse.

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## MYASTHENIA GRAVIS

E. P. Bharucha

*Natural Course of Myasthenia Gravis* : Fergusson et al (1955) have followed 75 cases for a period of 10 years and their results are given below :

60 Survivors (39 females and 21 males)—

Complete remission	.. 12 cases	} 47 cases (78% survivors)
Minimal symptoms	.. 17 cases	
Ocular myasthenia	.. 18 cases	
Moderate disability helped by neostigmine	11 cases	} 13 cases (22% survivors)
Critical condition despite neostigmine	2 cases	

15 Cases : 9 deaths (3 unrelated conditions, 3 myasthenia, 2 thymoma and 1 unknown), 6 untraced.

Fergusson considers those cases which remained confined to the eyes for many years, of good prognosis and calls the condition 'Benign Ocular Myasthenia'. 32 patients of Fergusson series had 81 remissions lasting for 4.9 years. He stresses the fact that complete spontaneous remissions are not uncommon in myasthenia gravis (at least 33 per cent of cases have spontaneous remissions).

**Thymectomy in Myasthenia Gravis :** The rationale of thymectomy lies in the observation of Wilson and Wilson (1955) that a curare-like substance can be extracted from the thymus gland, which interferes with neuromuscular transmission. Keynes (1954) found considerable improvement in 200 cases (excluding thymomas) on whom thymectomy was performed. American reports stress—

1. That thymectomy is beneficial in female myasthenics under 50 with a history of disease of less than ten years.
2. No definite benefit occurred in males, and therefore the procedure is contraindicated where the disease starts after 30 years of age.
3. Patients who have thymomas (15 per cent of all myasthenics) derive no improvement from thymectomy.

**Medical Management of Myasthenia Gravis : Drugs :** 1. Pyridostigmine bromide (Mestinon) presented in 60 mg tablets. This drug has less muscarine effect, viz. abdominal pain and diarrhoea and less nicotine effect, such as muscle cramps ; it has a prolonged action at night allowing of a full night's rest. Usually it is combined with neostigmine on 1:1 or 1:2 basis. It is however, ineffective when a patient becomes resistant to neostigmine.

2. Tensilon (edrophonium chloride): This is a short-acting anticholinesterase which helps in establishing the diagnosis of myasthenia gravis. 0.2 to 1 c.cm are given intravenously (2 to 10 mg) and if strength returns, the diagnosis of myasthenia gravis is established. If fasciculations occur and weakness persists, the case in question is not one of myasthenia gravis.

**Management of a Myasthenic Crisis:** Failure on the part of a myasthenic to clear secretions or breathe adequately should raise in the mind of the attending physician a possibility of a myasthenic crisis. This is usually due to unrecognised or inadequately treated myasthenia gravis. Occasionally, however, it may result from some development of prostigmine resistance and the consequent over-administration of this drug, resulting in what is now recognised as a 'cholinergic' crisis. Though the latter usually presents with abdominal pain, vomiting and muscle fasciculations, these may all be absent and presenting symptoms may be sudden simultaneous respiratory and deglutition paralysis.

The appearance therefore, of deglutition or respiratory difficulties in myasthenics should be followed by intubation or a tracheotomy with suction to clear the secretions and oxygen administration. If the respiratory weakness is predominant the patient may be put into the respirator. If secretions are excessive with myosis or slow pulse, 1.2 mg of atropine should be given intravenously and repeated if the condition improves. If there is no improvement Tensilon 0.2 c.cm (2 mg) intravenously should be given. If muscle fasciculations appear, the crisis is probably 'cholinergic'. If after 30 seconds, no effect has occurred another 0.8 c.cm (8 mg) of Tensilon is given and if recovery of strength occurs, the condition requires further treatment with cholinergic drugs. Mestinon is very useful as it causes less griping. While the patient is in the respirator, fluids and drugs should be given intravenously and when the patient comes out, tube feeding should be resorted to.

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## MYCOLOGY

H. S. Andleigh

The importance of fungus diseases has been mounting up recently as more and more cases of important fungus diseases are coming to light.

Medical mycology in India is as yet not a fully developed subject. Till about five years back, medical mycology was of interest mostly to the dermatologist and was limited to the study and identification of the dermatophytes. It is only during the last 4-5 years that much interest has awakened in the systemic fungus diseases. Much greater progress however has been made in mycology in other countries of the world during the last few years.



## Mycology

In India, Andleigh in 1952 described a case of chromoblastomycosis and pointed out the probability of chromoblastomycosis occurring in India, being in the same latitude as other areas of its incidence. He also pointed out that the disease had not till then been reported from continental Asia.

Kakoti and Dey (1957) reported a case of chromoblastomycosis of the female genitals. The diagnosis was confirmed by culture which yielded the growth of *Hormodendrum compactum*. Metastases, which are rare in these cases, were noticed in the regional lymph nodes.

Thomas et al (1957) reported a case of chromoblastomycosis in a 35 years old man with verrucous lesions on the right foot for a period of over 12 years. Clinical and histological features closely resembled those of chromoblastomycosis and cultural examination of the discharge yielded growth which the authors thought was *Hormodendrum compactum*.

Ajello (1956) studied specimens of soil from widely scattered geographic areas for the presence of human pathogenic fungi. Systemic fungi were isolated by intraperitoneal injection of soil supernatants into mice and subsequent cultivation of the liver and spleen while dermatophytes were recognised by baiting plates of moistened soil with filaments of sterilised human hair. Pathogenic species isolated included *Allescheria boydii*, *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum* and *Microsporon gypseum*. It was concluded that soil was an important reservoir of pathogenic fungi.

Das et al (1956) reported a case of coccidioidomycosis in India. The patient was a 29-year old woman with suppurating granulomatous lesions all over the body. The general clinical picture suggested actinomycosis but the characteristic "sulphur granules" were not found in the pus. The diagnosis of coccidioidomycosis was based on the discovery of "large round bodies about 4-5 times the size of a pus cell" which had a double-contoured wall and enclosed smaller bodies inside. In the photograph the cells do not resemble those of *Coccidioides immitis*. No cultural examination was done and no skin or serological tests were done. The diagnosis of the case appears to be doubtful.

Leeary et al (1956) presented a review of 100 cases of pulmonary coccidioidomycosis. Symptoms referable to the respiratory system were present in 83 and physical signs of pulmonary disease in 22 and of extrapulmonary disease in 7.

The radiological pattern in the lungs was cavitary in 56, nodular in 34, infiltrative in 8, pneumonic in 8, miliary in 4, pleural effusion in 2; hilar lymphadenopathy was seen in 7 cases.

*C. immitis* was isolated from 41 cases only. Serological tests were positive in others. No treatment was of any value.

Pinto (1957) described a case of pulmonary blastomycosis in a Hindu male resident in Bombay. The report is rather incomplete. The sputum contained budding yeast cells, culture was identified as blastomyces. Microscopic and culture reports are incomplete and in view of the incomplete microscopic and cultural examinations, it is difficult to be certain that this was a case of blastomycosis. In fact no true case of blastomycosis has been reported from India as yet.

Sen and Ghosh (1956) carried out a study to determine the incidence of histoplasmosis in 4855 patients who showed signs of lung infiltration but had a negative tuberculin test.

In addition to the history and clinical examination, fluoroscopy was done and skiagrams were taken when indicated. All the patients were tested with tuberculin, simultaneously and on the same forearm. 0.1 c.cm of a one per cent solution of histoplasmin was injected intracutaneously. The time of reading and the standard of reaction were the same as those of the tuberculin test. Sputum samples of patients who had a positive histoplasmin test were examined for *H. capsulatum* in some cases. In a few cases sternal marrow aspirations were made for the same purpose. Sputum from all the patients was examined for tubercle bacilli. Twenty six of the patients had a positive histoplasmin test, 3881 had a positive tuberculin test, 33 had a positive reaction to both the tests, and 915 had a negative reaction to both. Of the 26 who reacted to histoplasmin 14 had pulmonary calcification, 3 had pulmonary infiltration, 8 had no definite lung infiltration or calcification and one had a large mediastinal shadow on the right side. No *H. capsulatum* could be isolated from any of these patients. A true case of histoplasmosis has not yet been reported from India so far.

Wahi in 1952 examined 957 children and adults at Agra for histoplasmin sensitivity and detected 19 reactors.

Taneja et al (1955) carried out histoplasmin skin test on 962 healthy soldiers from different parts of India and 9 out of these developed a reaction of 10-19 mm. Some reactors were tuberculin negative but all showed pulmonary calcification, peribronchial thickenings and hilar densities in the Roentgenograms of the chest. Edwards (1956) examined a total of 2341 children and adults in Darjeeling and other districts of Assam. At Darjeeling 0.2 per cent had a reaction of 10 to 14 mm. The authors concluded that histoplasmin sensitivity did not occur in India.

Panja and Sen (1954) recorded one case of dermal histoplasmosis, but the evidence was only microscopic. Kalra et al (1956) isolated two strains of histoplasma. One strain was recovered from soil and the other from the sputum of a case who showed Roentgenological evidence of infection in the lungs.

Banerji and Gupta (1956) reported a case of unusually severe respiratory infection. In addition to the bacterial flora in the sputum, fungus-like organisms identified by bacteriological and biochemical tests to be a strain of *Candida albicans* were present. A remarkable response was obtained with Aureomycin. The isolated strain of *Candida albicans* showed no susceptibility *in vitro* to Aureomycin or any of the common antibiotics. It appears that *Candida albicans* played no important role in the pathogenesis of this acute respiratory disease.

Recently Kerschstern and Sidaransky (1956) reported a case of mycotic endocarditis of the tricuspid valve due to *Aspergillus flavus*. They suggested that ordinarily non-pathogenic fungi may produce fatal infections in debilitated persons who have been treated with broad spectrum antibiotics in massive doses.

Species of aspergilli are frequently isolated from patients with disease of the lungs and the fungi are generally regarded as contaminants. Recent work has shown that in a few instances species of aspergilli may actually be pathogenic. A new type of involvement of the lungs by aspergilli that results in characteristic clinical, radiological and pathologic findings has been described. In this type of lesion there is an entangled mass of hyphae in an epithelial-lined space that communicates with a bronchus. The radiological examination usually reveals a rounded density that is capped by a crescent of air. Patients frequently complain of only haemoptysis or they may be asymptomatic. Vellois et al (1957) reported such an interesting case of bronchial aspergillosis occurring as an intracavitary "fungus ball". The patient was clinically asymptomatic.

Gentles and Holmes (1957) studied the cause of spread of ringworm in coal miners. The most important factor in spreading dermatophytoses of the feet was the use of communal baths. All other factors were of minor importance.

Hickey (1956) described three cases of mycetoma of an unusual form involving the bones of the skull. All were of the yellow variety, possibly caused by *Nocardia somaliensis*. Slade et al (1956) carried out therapeutic trials with Terramycin on six patients of Maduromycotic mycetoma (black grain type) and 5 doses of 2 g of Terramycin were given. There was slight improvement in 4 cases of maduromycotic type and 4 cases of actinomycotic type but the improvement was only temporary.

From a study of recent literature on dermatomycosis, it is clear that the incidence of mycotic skin infections has been on the increase during the last few years.

Andleigh (1957) tried to grow *Malassezia furfur* on various special media with a view to find out some fungicidal agent against this fungus. The fungus could not be grown on any media.

Andleigh (1955) carried out investigations on the aetiology of pulmonary mycotic diseases. Sputa from 125 cases, radiologically and clinically pointing to a diagnosis of pulmonary tuberculosis but with sputum microscopically negative for acid-fast bacilli, were investigated. From two cases actinomycetes were isolated, one case was due to the anaerobic *Actinomyces bovis* and the other due to *Nocardia asteroides*. From two cases *Candida albicans* was isolated on repeated culture. *C. albicans* was also isolated from the bronchial aspirates of these cases.

Andleigh (1957) carried out investigation into the role of fungi in pulmonary suppuration. Complete mycological examination of 18 sputa from cases of pulmonary suppuration was carried out. *Actinomyces bovis* was isolated from one case and *C. albicans* from three cases. He suggested that sputum from all cases of pulmonary suppuration not responding to the usual antibiotics should be cultured.

## Mycology

On the diagnostic side the incorporation of cyclohexamide (Actidione) in the medium has made the isolation of all pathogenic fungi, excepting the cryptococcus, very much easier.

The addition of penicillin, 30 units per ml, and of streptomycin 40 units, or of only Chloromycetin 40  $\mu$ g per ml of the medium, after autoclaving, has been found to reduce the number of bacterial contaminants. Gridley's (1953) modification of the periodic-acid-schiff method of staining has made the demonstration of fungi in the tissues very much simpler. The complement fixation test for histoplasmosis, precipitin test for coccidioidomycosis and agglutination test for sporotrichosis are of recent development and of great value as diagnostic procedures.

Serological tests are important in the diagnosis of coccidioidomycosis. Smith et al (1956) studied the pattern of 39,500 serologic tests in cases of coccidioidomycosis occurring in the U.S.A. They found that specific precipitins appeared in the blood at an earlier stage of the infection but were transient and the precipitin test was of little value after the fifth month. The complement fixing antibodies appeared at a later date than the precipitins and were an indication of progressive infections, but even in clinically manifest primary pulmonary coccidioidomycosis the serological diagnosis in about one third of the cases must rest entirely on the precipitin test. However, precipitins were rarely found in disseminated infections and were almost unknown in relation to coccidioidal pulmonary residuals with or without cavitation. The complement fixing antibodies appeared usually during the first 3 months and a few reversions occurred by the second month. The titre of complement fixing antibody was generally a measure of the severity of the infections and titres in excess of 16 or 32 usually indicated the probability of dissemination.

The presence of antibody in C.S.F. is an indication of coccidioidal meningitis, as these antibodies do not pass through the blood-brain barrier. They do however pass through the placenta from the maternal to the foetal circulation and they may persist in the blood of the infant for some months. Congenital coccidioidomycosis is however not known to occur.

Recently much progress has been made in the search of antifungal agents. Among the aromatic amines, stilbamidine has been found effective against North American blastomycosis.

Rhodandine, an organic sulfur compound, has been found very effective in cases of histoplasmosis.

Andleigh (1957) carried out *in vitro* sensitivity tests with aromatic amines pentamidine and stilbamidine against the organisms isolated from cases of maduromycosis in India. Pentamidine in a concentration of 0.1 mg per ml of the medium inhibited the growth of *Madurella mycetomi*. Stilbamidine did not give any encouraging results.

Further studies by Andleigh (1957) with hydroxy-stilbamidine isethionate and 4 : 4 diamidine-diphenylamine dihydrochloride (M & B 938) against *Madurella mycetomi* which was isolated from about 80 per cent of cases of maduromycetoma, showed that *Madurella mycetomi* was very sensitive to M & B 938 as a fungicide. Clinical trials with these medicines are now being carried out.

Andleigh (1955) studied the sensitivity of actinomycetes against penicillin and other antibiotics and found that streptomycin was slightly more effective than penicillin against the pathogenic actinomycetes.

Two antibiotics recently found to be effective against fungi only are cyclohexamide (Actidione) and Nystatin and both are produced by the same species of streptomycetes, called *Streptomyces noursei*. Both the agents are strong fungistatic and fungicidal agents.

Actidione has a much narrower spectrum than Nystatin among the pathogenic fungi; Actidione is active in therapeutic doses only against *Cryptococcus neoformans* but nystatin is active against *Candida albicans*, *Blastomyces dermatitis*, *Histoplasma capsulatum*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, *Aspergillus fumigatus* and *Sporotrichum schenckii*.

Andleigh (1957) studied the fungicidal activity of mycostatin (Nystatin) against *Candida albicans*. Heilig and Andleigh (1957) reported a case of bronchopulmonary moniliasis treated with mycostatin. Andleigh (1957) treated a case of monilial onychomycosis with mycostatin.

Andleigh (1957) studied the fungicidal activity of mycostatin against organisms causing maduromycosis in India. Mycostatin was found to have no fungicidal activity against *Madurella mycetomi*.

Mycostatin has now been found to be effective in all forms of moniliasis.

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## MYOCARDIAL BLOOD SUPPLY, ANATOMY OF

S. L. Robert

The musculature of the heart is the most important vascular bed in the body. It is estimated that at least two thirds of all heart diseases and heart failures arise from a relative or absolute failure of its vascular system.

Schlesinger's<sup>22</sup> work established the fact that the distribution of the two coronary arteries which supply blood to the myocardium conforms to three distinct patterns. The following details about their distribution are largely based on Gregg's<sup>7</sup> and Rushmer's<sup>20</sup> descriptions.

- (a) Right coronary preponderant—48 per cent. In this pattern the right coronary artery supplies all the right ventricle, the posterior half of the interventricular septum and a large part of the posterior wall of the left ventricle.
- (b) Balanced coronary distribution—34 per cent. In this the right artery supplies only the right ventricle and the posterior half of the interventricular septum and the left supplies the left ventricle and the anterior half of the interventricular septum.

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- (c) Left coronary preponderant—18 per cent. In this the left may supply the whole of the left ventricle and the interventricular septum, in addition it may also supply a part of the right ventricle over its posterior surface and anteriorly in the region around the pulmonary conus and on the right ventricular side of the left descendens.

The sinoatrial node is supplied by a branch of the right coronary artery in about 70 per cent of hearts and by a branch of the left coronary in 20 per cent and in 7 per cent from both the vessels. The auriculo-ventricular node is supplied by the right coronary in about 92 per cent of hearts. The right bundle branch generally obtains its blood supply from the anterior descending branch of the left coronary artery but may be supplied by right and left coronary arteries. The left bundle branch is generally supplied by both arteries usually from septal branches of the left anterior descendens branch and small vessels from the right coronary artery. The descending branch of the left coronary artery is the one which is most frequently thrombosed and so it has been called the "artery of sudden death".

Anomalies of origin are not uncommon. The most frequent major coronary artery anomaly is one in which the left artery or its anterior descending branch arises from the left pulmonary artery or conus and supplies the left ventricle with venous blood. Amongst the other anomalies may be mentioned: the right or both arteries arising from the pulmonary artery, the coronary arteries originating anywhere on the ascending aorta and one or both the arteries being hypoplastic.

The coronary arteries break up into sub-epicardial, muscular and endocardial twigs communicating with each other and then drain via capillaries into the cardiac veins but they are also in direct communication with the cardiac chambers by means of:

- (a) Arterio-luminal branches, 0.2 to 1.0 mm in diameter.
- (b) Arterio-sinusoidal branches, 50-250 micra in diameter.

The capillary counts are considerably higher in the ventricles than in the auricles and the neuro-muscular bundle.

Gregg<sup>8</sup> who has thrown much light on the venous drainage of the myocardium has recently (1955) surveyed the literature on coronary circulation.

The venous drainage systems of the heart are:

- (a) The superficial or sub-epicardial system which empties into the right auricle through the coronary sinus and the anterior cardiac veins. (As a rare anomaly the coronary sinus may open into the left auricle or communicate with both the auricles).
- (b) A deep system of veins which communicates directly with the heart chambers.
- (c) Thebesian veins—the least cardiac veins which arise everywhere within the heart musculature.

Writing about the thebesian veins Hollinshead<sup>10</sup> says that they anastomose with the coronary venous system and that most of the blood through them passes into the chambers of the heart, though some may pass outward into the coronary veins. He concludes that presumably the flow in them can be reversed and aid in revascularizing an ischaemic heart.

Butterworth<sup>2</sup> has recently shown that venous blood also drains partly into the left auricle via the thebesian veins.

Truex and Armand<sup>27</sup> have demonstrated a venous network within the myocardium of the left ventricle and the interventricular septum which is far greater than that of the right ventricle.

According to Bard<sup>1</sup> practically all the flow into the coronary sinus arises from the left coronary artery, a small portion of left inflow and a very large part of right inflow are drained by the anterior cardiac veins and a very small portion of blood from the right coronary artery drains into the coronary sinus.

Intracardiac anastomotic channels exist connecting the coronary veins of auricles and ventricles with each other, with thebesian channels and with extracardiac veins draining into the superior and inferior vena cava. Evidence has recently been brought forward by Prinzmetal, Myron, Simpkin, Bergman and Kruger<sup>18</sup> to show the presence of myocardial glomera or small arterio-venous anastomoses.

Besides the intracardiac anastomoses, there are also extracardiac anastomoses between auricular twigs of the coronary artery branches and branches of arteries surrounding the heart

namely, internal mammary, anterior mediastinal, pericardial, phrenic, intercostal and oesophageal as demonstrated by Hudson, Moritz and Wearn<sup>12</sup>. Some of these routes are now being utilized by surgeons for supplementing blood supply to an ischaemic myocardium.

The coronary arteries are commonly described to be functionally albeit not anatomically endarteries. Grant<sup>6</sup> however states that there are no endarteries in the heart. The main branches of the coronary arteries anastomose with each other and so do the capillaries and precapillaries. Moreover anastomoses improve with age, the channels becoming wider, and in the epicardial fat they apparently increase in number. He also cites the conclusions of various workers and goes on to state that, as the coronary sinus and veins of the heart have no adequate valves, it is not impossible that the blood may take a retrograde course in the veins, irrigate the myocardium and enter each of the four chambers via the thebesian veins. Hollinshead<sup>10</sup> also states that the venous valves may become incompetent if exposed to any considerable amount of back pressure and it is thus possible to reverse the usual direction of flow in the coronary veins. Advantage is being taken of this fact also in attempting to increase by surgical means the arterial flow to the heart muscle.

Whenever relative anoxaemia of the heart muscle develops as a result of slow narrowing of the coronary arteries collateral circulation develops sufficiently to prevent myocardial infarction. This is confirmed by Zoll, Wessler and Schlesinger<sup>30</sup> who on the basis of their work conclude that relative cardiac anoxaemia is the stimulus which produces the development of anastomoses between the coronary arteries. Fishman and Cournard<sup>4</sup> have further stated that the formation of inter-coronary anastomoses is also stimulated by anastomosing the internal mammary artery to the ventricular myocardium.

As regards the question of nervous control of the coronary flow Rushmer<sup>20</sup> states that it is currently believed that the calibre of the coronary vessels depends upon a state of constrictor tone produced by a continuous vagal discharge and that coronary vasoconstriction is released by reducing vagal discharge and to a lesser extent by increasing either sympathetic stimulation or circulating epinephrine. Mitchell<sup>16</sup> states that the majority agree that the parasympathetic activity is associated with vasoconstriction and sympathetic activity with vasodilatation of the coronary circulation.

Impairment of the blood supply to the heart muscle may manifest itself in a variety of syndromes varying from sudden death to various degrees of disability. The two major conditions associated with it are angina pectoris and coronary occlusion. The pain of angina is evidently directly related to anoxaemia of heart muscle and consequent accumulation of metabolic products.

The fundamental cause of blood impairment to heart muscle is arteriosclerosis of the coronary arteries which brings on coronary insufficiency. This term "coronary insufficiency" has been discussed in great detail by Scherf and Golbey<sup>21</sup>. They say that it should not be considered a diagnosis any more than the term 'anginal pain' and that its cause and mechanism should be sought.

One good test to assess coronary insufficiency is the anoxaemia test. Stewart and Carr<sup>25</sup> writing about the anoxaemia test state that approximately 25 per cent of patients with coronary artery disease who suffer from angina pectoris have no objective evidence of heart disease. The anoxaemia test has been designed to provide objective evidence of the presence of coronary insufficiency. Cosby, Talbot, Levinson and Mayo<sup>3</sup> state that acute coronary insufficiency is a common clinical entity, at least half as common as acute transmural infarction, and that vector electrocardiography is of real value in acute coronary insufficiency and in acute myocardial infarction.

In order to improve the blood supply to the myocardium when it has become reduced, medical as well as surgical measures are employed. Among the medical measures are drugs such as glyceryl trinitrate, papaverine, peritrate, hormones, anticoagulants and radioactive iodine. Maloney and Blalock<sup>15</sup> think that the recent discoveries in the fields of lipid metabolism and the genesis of arteriosclerosis also offer the hope that coronary disease may in future be prevented rather than treated after it develops.

Surgical measures based on anatomical considerations are also now being used extensively :

- (a) For improving blood supply to heart muscle suffering from coronary insufficiency and

## Myocardial Blood Supply, Anatomy of

- (b) For keeping the coronary circulation going when cardiac pump action for cardiac surgery must be temporarily dispensed with either by hypothermia or by open technique in which the heart and lungs of a normothermic patient are bypassed by a mechanical pump oxygenator.

For improving the blood supply to an ischaemic myocardium, Thompson and Plachta<sup>26</sup> after fourteen years' experience with cardiopexy done by spreading 2 to 4 drs. of dry magnesium silicate powder over the surface of the myocardium, state that for a group of patients, who were medical failures, this operation has produced most satisfactory results. Key, Kergin and Martineau<sup>13</sup> have reported on the use of jejunal pedicle graft with possible advantages. Vineberg, Munro, Cohen and Buller<sup>28</sup> have got most encouraging results from internal mammary artery implantation and Vineberg and Buller<sup>29</sup> have described the technical factors which favour mammary coronary anastomosis with a report on 45 human patients with very satisfactory results.

Leighninger<sup>14</sup> reports relief of symptoms to a significant degree in nine out of ten patients by Beck No. 1 operation consisting of partial coronary sinus ligation, epicardial abrasion, intrapericardial instillation of asbestos powder and approximation of mediastinal fat to the heart. Selman<sup>23</sup> reports 85 per cent of surviving patients being benefited by Beck No. 2 operation (though considered less desirable than Beck No. 1) consisting of a vein graft from the aorta to the coronary sinus followed in three weeks by partial ligation of the sinus. Glover<sup>5</sup> has recently described a simple procedure of severing and tying off of both internal mammary arteries which has brought about immediate relief to 12 of 13 patients suffering from coronary insufficiency and intractable angina. The operation is in an experimental stage and much more research must be done to prove its efficacy and mode of action. This operation makes use of the anastomoses between the branches of the internal mammary arteries and the coronary arteries. The Montreal Medico-Chirurgical Society<sup>17</sup> has also reported encouraging results from internal mammary artery implantation into the ventricular myocardium amongst 88 cases.

As regards keeping the coronary circulation going when the heart has to be temporarily stopped, hypothermia (for cardiac occlusion) was considered hazardous because of the possibility of ventricular fibrillation. Shumway, Gliedman and Lewis<sup>24</sup> have demonstrated that coronary perfusion with arterialized blood was effective in sharply reducing its incidence. Further Riberi, Siderys and Shumacker<sup>19</sup> have demonstrated the role played by the autonomic nervous system in the production of ventricular fibrillation in hypothermia and the effectiveness of sino-auricular node blockade preventing its occurrence. Grow, Demong and Hawes<sup>9</sup> have described a method utilizing selective coronary perfusion and hypothermia for cardiac surgery on 10 human cases.

Catheterization of the coronary arteries in the intact animal has also been successfully accomplished in 12 animals by Horvath, Farrand, Blatteis and Everingham<sup>11</sup> and the potential application of this technique to further the understanding of cardiac dynamics has been thereby illustrated.

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## MYOCARDIAL INFARCTION, INCIDENCE IN INDIA

O. T. Samani

A couple of surveys available in our country in the last decade agree with the Western ones that males are more often affected than females.

Parkinson and Bedford<sup>4</sup> in their report on 83 post-mortem cases of myocardial infarction report 72 males and 11 females. Bland and White<sup>1</sup> in a series of 200 clinical cases of myocardial infarction report 84 per cent males and 16 per cent females. Of the younger age group (below 40 years) Glandy, Levine and White<sup>3</sup> found 96 males and 4 females in a group of 100 cases who had experienced myocardial infarction before the age of 40 years. In the same age group Gertler and others<sup>2</sup> also in the U.S.A. found 97 per cent males and 3 per cent females. Similar studies in our country showed in Vakil's series of 115 cases as 90.4 per cent males and 9.6 per cent females.

**Sex Distribution (208 Cases) :** In the author's series of 208 cases from Bombay<sup>5</sup> sex distribution was : 196 cases (94.2 per cent) males and 12 cases (5.8 per cent) females. The relatively high male incidence may be due to lesser number of Muslim females coming forward for hospitalization compared to the males.

**Age Distribution:** "Myocardial infarction" is a disease of later decades of life although no age is exempt from coronary artery disease. Average age of onset in one U.S.A. series (Bland and White—1936) was 56.2 years. In Vakil's series (1949)<sup>6</sup> of 115 cases peak period was 40/49 years (40 per cent), of these 19 cases (16.4 per cent) were below the age of 40 years. In the author's series of 208 cases the peak period of incidence was found in the age group 41-50 years (32.8 per cent). Thus peak period of incidence of myocardial infarction like coronary heart disease in general in our country, especially on the West coast, reaches at least 10 years earlier compared to the West.

In young adults (below the age of 40 years) in the present series of 208 cases, myocardial infarction was noted in 26.9 per cent compared to 4.2 per cent in White and Bland's series (1936) of 461 cases and 16.4 per cent in Vakil's series (1949) of 115 cases. The difference of about 10 per cent in the two samplings from the same city may be due to aetiological factors other than atheroma prevalent in this part of the city. The "male to female" ratio was 16.3:1;



## Myopathies and Polymyositis

preponderance of males over females is maintained in all individual age groups, age group 41-50 years shows "male to female" ratio at its highest viz. 70:0 and percentage of females was relatively higher in older age groups.

In the author's series of 208 cases there were 45.6 per cent Muslims, 32.7 per cent Hindus, 16.3 per cent Christians, 1.9 per cent Parsis and 3.5 per cent others. Predominance of Muslims as explained by the author has been due to the particular location of the hospital.

As for young adults below the age of 40 years, there were 11.1 per cent Hindus, 14.4 per cent Muslims, 2.4 per cent Christians and 0.5 per cent others. Of these the majority belong to the age group 31-40 years.

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## MYOPATHIES AND POLYMYOSITIS

J. B. Mehta

No significant advance has been made in the direction of aetiology or treatment of the myopathies. The chief advance has been in the clinical and pathological distinction between the true genetic myopathies and polymyositis, which so superficially resembles myopathy. It has for long been known, even from Erb's time, that isolated cases of myopathies made unexpected spontaneous recoveries. Nattras and Walton<sup>3,4</sup> studied eight such cases and Walton and Adams forty such cases<sup>4</sup>. Whilst these cases resemble various types of myopathies strongly and in fact were initially diagnosed as myopathies they found certain distinctions which helped in making the true diagnosis of polymyositis. The onset may be acute, subacute or chronic. True myopathies are almost always chronic and progressive. Polymyositis may occur in childhood or adult life ; family history is negative. The disease may run a rapid, acute and fatal course, or there may be periods of remission with ultimate recovery. Many of these changes are associated with skin changes of dermatomyositis or lupus erythematosus, rheumatoid arthritis and other collagen diseases. The association of polymyositis with cancer is another feature of note. Muscles of deglutition may be affected.

Electromyography often confirms the diagnosis. True myopathic and neuromyopathic patterns are distinguishable<sup>2,4</sup>.

Muscle biopsy, however, seems to be the final diagnostic answer<sup>1,3,4</sup>. Microscopically the muscles vary in size in polymyositis and a central migration of the sarcolemmal nuclei, necrosis, phagocytosis with cellular infiltration and hyalination are distinguishing features. Evidence of muscle "regeneration" is seen. Walton, however, emphasises that while these changes are usual they are not specific and must be taken into consideration only together with clinical findings. Nattras however, lays greater stress on its diagnostic value. Adams and Denny-Brown emphasize that muscle biopsy must be from the affected muscles. The technic is also important. Crushing, tearing, twisting of specimen are to be avoided<sup>1</sup>.

Polymyositis responds favourably to ACTH, cortisone and vitamin E or wheatgerm oil<sup>1,4</sup>. Animal experiments have shown that vitamin E deficiencies and to some extent vitamin A and vitamin C deficiencies produce histological pictures in muscles similar to polymyositis. This picture is also seen in some virus (Coxsackie) infections and plasmocid intoxication<sup>1</sup>.

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**MUSCULAR CONTRACTION, ROLE OF POTASSIUM IN—**See POTASSIUM, ITS ROLE IN BODY FLUIDS AND MUSCULAR CONTRACTION

**NASAL ACCESSORY SINUSES—**See NOSE AND NASAL ACCESSORY SINUSES

## NEPHRITIS AND NEPHROSIS

The study of renal diseases has been advancing considerably in recent times on account of the more modern methods of advanced physiological research, renal biopsy and renal angiography, electron microscopy and autoradiography. Radioactive isotopes have helped to assess the composition and the size of the affected water compartments of the body, and chromatography has helped to assess supra-renal corticoid function in regard to the essential metabolism of sodium and water—an essential knowledge required in an understanding of renal diseases. The two important conditions under review, viz. nephritis and nephrosis include orthostatic albuminuria, prerenal azotaemia, pre-eclampsia, essential hypertension, particularly in its malignant phase and possibly pyelonephritis. How they are related will be evident from the fact as reported by Dieckmann in 1953 that an anuric patient if infused with normal saline, develops signs indistinguishable from eclampsia. If nephritis and nephrosis go into a chronic stage, chronic glomerulonephritis with hyalinization of the glomerular membrane is the common termination—an end equally revealed even in essential hypertension.

Volhard had advanced the concept as quoted by Fishberg in 1952 that renal haemodynamic changes were responsible for disorders of renal function and this thesis has been supported by many recent investigations. It is now conceded that renal vein backpressure, hitherto strongly suspected as an aetiological factor in orthostatic albuminuria is equally responsible in the nephrosis consequent to renal vein thrombosis. De Carvalho's (1954) experimental data indicate the existence of an altered intrarenal circulation resembling renal vein back pressure, whilst Trueta's (1948)<sup>30</sup> experiments explain an interference with the arterial supply to the viscus.

Hall (1953)<sup>15</sup>, Pease (1955)<sup>22</sup> and Rhodin's (1956)<sup>25</sup> experimental study with electron microscope provided us with new knowledge on the structure of the renal basement membrane. These findings contradict renal pathology built on intercapillary changes.

Renal physiology has advanced recently and thrown new light in the study of renal pathology. In this connection De Carvalho and Trueta's studies mentioned above have come to us as great help. Trueta mechanism suggests an active renal arterial spasm, whilst De Carvalho's data demonstrate a possible back flow into the renal veins. Thal in 1955<sup>29</sup> has shown that staphylococcal toxin produced in the rabbit kidney a temporary vasospasm, lasting some hours, which arrested the circulation in the cortical glomeruli and in the outer cortical zone—often with consequent bilateral cortical necrosis—but which did not impede the blood flow in the juxtamedullary glomeruli.

Regarding the experimental production of nephritis Gaunt and Rienzi (1954)<sup>14</sup> have produced in rats a condition comparable to acute glomerulonephritis or to its equivalent, eclampsia, affording good opportunity to study its pathology. The data obtained by this study was confirmed by similar study by Page and Glendenning (1955)<sup>20</sup>, Daniel, Prichard and Ward-McQuaid (1954)<sup>7</sup>. The data suggests that renal artery spasm can result in a syndrome comparable to acute glomerulonephritis or eclampsia, if renal cortical ischaemia had been produced by corticoid and salt sensitization.

Pressman (1953) has confirmed earlier work that a nephrotoxic action is invariably present in all types of antisera available, be they primarily directed to the liver, lung, aorta, placenta or the kidney. It is clear that these sera damage many organs simultaneously. The antirenal sera have been shown to produce in animals a clinical state corresponding to nephrosis or nephritis depending on their dosage—the latter requiring the lesser amount. He, by impregnating the antisera with radioactive iodine, has shown by autoradiography that the radioactivity is confined entirely to the glomerulus and that none filters through to the tubule. This suggests that either a nephrotoxic substance combines with the glomerular tissue and, or, that a temporary haemodynamic change, viz. an ischaemic spasm has been evoked by the nephrotoxin completely preventing its filtration through the glomerular capillaries into the tubules, thereby limiting its effect.

Distinction between nephritis and nephrosis is still controversial. Nephrosis is said to be the case when albuminuria and oedema dominate the picture and hypoproteinaemia, hypercholesteraemia and lipiduria occur, and even though red cells and casts may occasionally be present in urine. But when hypertension precedes, accompanies or terminates its course and renal failure is the end result, then only confusion arises with nephritis. Although nephritis is held to be inflammatory, the reliance on anatomical changes to explain the condition is slender as has been proved by recent investigations.

## Nephritis and Nephrosis

While causes such as diphtheria and syphilis are no longer considered important in the production of nephritis and nephrosis newer factors are encountered which can be regarded as producing allergic manifestations. In this connection Luetscher, Piel and Curtis (1955)<sup>17</sup> state that a large proportion of nephrotic patients have a history of allergy of some severity, often related in time to the development of oedema, and many show striking eosinophilia. X-rays have been found to be causative also. Allen (1955)<sup>1</sup> has recently put forward the view that nephrosis is a complication of many diseases and abates when these terminate. He has based his theory on the post-mortem evidence of nephrosis in patients dying of cancer, in whom no nephrotic manifestations had been detectable in life. The association of diabetes, amyloidosis and lupus erythematosus with nephrosis has been further confirmed. A better understanding of the aetiology has been emphasized on its association with renal vein back pressure as in renal vein thrombosis, revealed by venography, and in constrictive pericarditis. It is in the latter condition that its dramatic reversibility is evident following pericardiectomy. A haemodynamic change could be suspected also in experimental allergy known to cause nephrosis. De and Sengupta's experiment (1951)<sup>8</sup> proving the evidence of shunting of blood from the cortex to the medulla under experimental conditions, may throw some light on this haemodynamic change.

Renal structural changes in nephrosis as studied by electron microscopy by MacManus (1950),<sup>18</sup> Allen and Fishberg (1952), Allen (1955)<sup>1</sup> and Muehrcke (1955)<sup>19</sup> by needle biopsy did not reveal any uniform result—as on occasion, no change in it was demonstrable. The tubular changes are late and affect the proximal tubule principally, the lumen is dilated and the lining cells usually flattened and contain lipid.

In renal vein thrombosis responsible for the nephrotic syndrome, no change in glomerular structure is detectable. Blainey, Hardwicke and Whitfield (1954)<sup>4</sup> cited three case records of high renal vein pressure. In two of the cases renal vein thrombosis had occurred and in the third pericarditis was responsible. Pericardiectomy in the last relieved not only the very high renal venous pressure maintained, but also every sign of the accompanying nephrotic syndrome.

It has been found in many renal diseases that clearances are proportional to the molecular size of the protein fraction and are characteristic of the diseases. Recently it has been demonstrated that in nephrosis albumin,  $\alpha_1$  and gamma globulin fall,— $\alpha_2$  globulin and cholesterol rise (Squire, 1953)<sup>28</sup>; in nephritis the relative clearances of  $\alpha_1$  and gamma globulin are greater (Hardwicke, 1954); and in renal vein thrombosis the clearances are as in nephrosis (Blainey 1954)<sup>4</sup>, which is to be expected.

ACTH prevents proteinuria in nephrosis and as such renal biopsy before and after its administration will show whether clinical improvement has been based on restoration of anatomical normality. Electron microscopy, by measuring pore sizes will also help such assessment. Fishberg regards the unnatural permeability of the glomerular wall as a non-inflammatory change which is not definitely recognizable microscopically at a stage when it has produced massive proteinuria.

The biochemical findings in nephrosis by various workers such as Fishberg (1952), Burke (1954), Allen (1955), Eder (1955), Smith (1955), and Luetscher (1955) etc. did not reveal any uniformity. Reflections on these findings suggest a great divergence in the pattern of the intrarenal blood circulation and that structural changes in the kidney could hardly be the responsible factor in producing them. A haemodynamic theory can only explain this. It has been variously advanced that there is a stagnation of blood in the glomerular capillaries which are in consequence abnormally distended. The stagnation would favour a reduced filtration of sodium and water, whilst dilatation would bring about an increased glomerular pore size. The stagnation can be due to renal haemodynamic changes such as are effected by renal venous back pressure accompanying renal vein thrombosis causing nephrosis.

Luetscher (1955)<sup>17</sup> produced much evidence to his conclusion viz. "the idea that nephrosis is a metabolic disease, perhaps arising in the adrenals, does not appear tenable." Changes in adrenocortical activity may modify the course of the disease. Their therapeutic effects are in keeping with the views as well.

Fishberg's (1954) conception of nephrosis is of a non-inflammatory disease of the nephron, including necrotizing nephrosis, chronic lipid nephrosis, diabetic glomerulosclerosis (Kimmelstiel-Wilson syndrome), amyloidosis and toxæmia of pregnancy. Such concepts

of nephrosis are based largely upon histological evidence of damage to different parts of the nephron ; but to many others (Kramer, Goldman and Casen, 1952) nephrosis is a clinical rather than a histological entity—as expressed in the following lines : “ Nephrosis occupies a position shared by few diseases in medicine ; its aetiology is unknown, its course unpredictable, its progress uncertain and its treatment unsatisfactory. Nevertheless, its cardinal manifestations—oedema, hypoproteinaemia, albuminuria and hypercholesteraemia are so striking, and the remissions and exacerbations at times so dramatic as to challenge the attention of both the clinician and the scientist”.

The cause of oedema has been much debated, and Merrill (1955) attached importance to adrenocortical dysfunction in the production of oedema. That ACTH can induce diuresis in such cases has been proved and explained by Allen (1955)<sup>1</sup>. It reduces permeability thereby reducing albuminuria, and increases glomerular filtration rate.

The other characteristic feature of nephrosis is lipiduria due both to cholesterol fatty acids and phospholipids ; there is also lipidaemia.

Cortical necrosis was found in anuria of pregnancy as far back as over fifty years ago. Recently, however, tubular necrosis has been described in some cases of anuria resulting from burns, mismatched blood transfusion and crushing injuries. This condition became known as “ lower nephron nephrosis ” or more accurately, “ tubular necrosis ”. Clinically it is almost impossible to say whether cortical or tubular necrosis is the underlying pathology in a given case. Prognostically of course, the two conditions may be different and it is important to note that the latter may be a reversible one whereas the former is not. Bull, Jeekes and Lowe's outstanding contribution (1949)<sup>2</sup> on this subject of tubular necrosis has been of great help to the clinician. This is divided into three stages, viz. precipitating stage, stage of oliguria or anuria and the stage of diuresis. The treatment for both is the same and recent work has been concentrated largely on the phase of diuresis and the control of potassium excess or deficiency is the crux of the problem (Fourman, 1953)<sup>12</sup>.

Regarding treatment of nephrosis the latest trials have been with malarial therapy. The idea arose from the fact that a few cases of nephrosis had profuse diuresis after being infected with measles. Gairdner and Shute (1955)<sup>13</sup> report the results of cases treated in this manner. Out of 65 cases they observed, there was three months' remission in 28 per cent. Long-lasting remissions can be expected in 25 per cent of such treated cases.

Treatment with steroid hormones, e.g. ACTH and cortisone, has received further support from many authorities, e.g. Greenman and Dankowski (1953) and Kramer (1955). Very recently prednisolone has been found to give very satisfactory results in nephrosis and nephritis (Bunim, Pechet and Bollet, 1955 and Arneil, 1956) ; similar results have also been reported by Friederiszick and Hoffacker at Mainz, Germany (1956), by Bertoni of Verona, Italy (1956) and Pasteur Vallery-Rodot, Laroche, Milliez and Lagrue of Paris (1956).

Renal tubular acidosis producing rickets and osteomalacia is also receiving greater attention and Singh and Jolly have recently (1957)<sup>27</sup> demonstrated two cases of renal tubular osteomalacia.

A new method of diagnosis of urinary tract infections has been reported by Schaus of Luxemburg (1956)<sup>28</sup>. He stated that the urine of healthy subjects contains a certain amount of nitrates which come primarily from the vegetable components of the diet. The presence of nitrites, on the other hand, always indicate infection by pathogenic micro-organisms. *E. coli* in particular but also staphylococcus, *B. proteus* and sometimes the typhoid bacillus have the property of reducing nitrates to nitrites, but not the streptococcus, gonococcus or the tubercle bacillus. The nitrites can be easily detected in the urine by simple tests.

Another important study made recently is what Rammelkamp et al<sup>24</sup> affirmed that there is strong evidence of specifically “ nephritogenic ” strains of group ‘ A ’ streptococci which commonly belong to type 12 to type 4 or to a new type. A striking point in Rammelkamp's work is that these nephritogenic streptococci undergo lysis after infection with a bacteriophage not usually lytic for other serological types. It is known that bacteriophage may convert avirulent diphtheria bacilli to toxigenic mutants ; and possibly a similar phenomenon determines the pathogenesis of nephritis. What has been discovered so far seems to indicate that in the causation of acute glomerulonephritis the peculiarity lies largely in the organism ; in rheumatic fever it may be in the host (Lancet, May 11, 1957, p. 979).

One of the most significant and interesting study made recently is the role of long continued milk diet and alkali treatment of peptic ulcer in the causation of nephrocalcinosis. Two such cases have been recently reported in the German press by Heintz (1956)<sup>16</sup>. Such incidence had however, been repeatedly reported in the Anglo-American literature under the name of "Milk-alkali syndrome" or "Burnett's syndrome" after Burnett who first described it in 1949. Dufault, Tobias and others also reported a similar entity under the name of "Milk-drinker's syndrome".

The development of artificial kidney has been further perfected and its clinical applications have been further reported. This has been used as a counter-measure in cases of anuria due to sudden renal failure, e.g., as a result of glomerular nephritis or mercurial poisoning. Bernier of Paris (1956) mentions that in patients suffering from barbiturate or bromide poisoning the artificial kidney may even act as a life-saver. The best results so far recorded have been obtained with Kollf's apparatus which is made of a plastic material and does not contain any metal parts. The blood is pumped through a semipermeable cellophane tube which is immersed in about 100 litres of wash fluid : the composition of this fluid varies depending on the case under treatment. The dialysing surface thus provided amounts approximately to 20,000 cm.<sup>2</sup>

By the use of artificial kidney it is also possible to normalise an excessive blood urea concentration or to overcome complex electrolyte disorders. Its use is contra-indicated in haemorrhage and within the first two days after an operation.

Besides the modified Kollf's apparatus there are two other available, one being modified "Alwall" and the other "Skeggs and Leonard 'flat sheet' artificial kidney".

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## NEPHROSIS—See NEPHRITIS AND NEPHROSIS

## NEUROPHYSIOLOGY

R. N. Sen

Our knowledge of neurophysiology as applied to clinical medicine has not sufficiently advanced since the readily available laboratory animals exhibit wide phylogenetic difference from man. Differences in the functions of brain in the various species are significant in the neocortex, but much less in the phylogenetically older autonomic nervous system. As such, emphasis has been given to this part of the brain in this paper.

Factors determining voluntary movements are of special significance in the somatic part of neurophysiology. Bubnoff and Heidenhain (1881) and Brown and Sherrington (1912) stressed that there is no sharp line of demarcation between the motor and sensory processes, based on their studies on the modifications of motor activity through proprioceptive and nociceptive impulses. Rade Maker (1948) illustrated the close integration of sensory and motor reactions in the visual sphere. Intimate relationship between sensory impulses and voluntary movements has also been stressed by many other workers. Walshe (1947) states that the "receptor system is initiating and directing willed movements". Goddy (1949) emphasized the loss of voluntary movements after lesions in the sensory parts of the cerebral cortex. Diffuse motor discharge which originates in the cerebral cortex produces voluntary movements and the same is sustained and modified to the proper pattern through proprioceptive impulses. Those afferent impulses which are below the level of consciousness also play a part in the performance of normal movements. Penfield and Rasmussen (1950) observed that stimulation of secondary motor area elicits intention movements.

von Frey (1926) has shown after elimination of impulses at the cutaneous nerve endings through anaesthesia, that the performance of skilled movements depends on more than one sensory modality.

Various somatic movements have been described on stimulation of different structures included in the limbic system of the brain (Macleán and Delgado 1953, Anand and Dua 1956, Kaada 1953). Muscles involved are the ipsilateral facial, eyelid, orbital and oral muscles. Kaada (1953) reported contralateral turning of the head on stimulation of the amygdala. Magnus et al (1952) stressed this movement as of diagnostic importance in temporal lobe epileptic seizures. Eating automatisms (licking, biting, chewing, etc.) were produced on stimulation of the lateral hypothalamus (Delgado and Anand, 1953) and after stimulation of all the limbic structures (Anand and Dua 1956).

Possible relationship between discharge from the motor cortex and from other parts of the cortex needs further clarification.

Discovery of the E. E. G. by Berger and subsequent studies on the relation of the hypothalamus to the waking state by Ranson and the researches on the problem of consciousness are of significant importance both to the neurologist and the general physician. Ranson assumed that the posterior hypothalamus is the centre of wakefulness and that a lesion in the posterior hypothalamus results in sleep. Hess believed that sleep is an active process and that it results from stimulation of certain diencephalic areas and not from pathological lesions. Investigations of Anand (1955) and Nauta (1946) have clarified the difference. They claim that lesions of the mammillary body of the posterior hypothalamus produce sleep.

Anand and Brobeck (1951) showed the presence of a "feeding centre" in the lateral hypothalamus and a "satiety centre" in the medial hypothalamus. Stimulation of these two centres in conscious animals leads to marked increase and decrease in the food intake respectively. Brobeck et al (1955) showed that amphetamine decreases appetite by increasing the activity of the "satiety centre" as recorded by E. E. G. with depth electrodes. Anand, Dua and Chhina (1957) have also shown in monkeys that the control over food intake is exerted from cortical regions. Frontal lobe lesions including those of the orbital cortex led to increase in food intake. They concluded that cortical structures have discriminative mechanism (appetite) whereas the primitive urge "hunger" originates at the hypothalamic level.

In the past the problem of consciousness was solely thought to be the function of the neocortex. Recently the work of Magoun (1952) and Penfield (1952) have brought out the role of brain stem 'activating mechanisms' and of the "centroencephalic system" in the mechanism of consciousness. These regions send impulses to the neocortex as well as the limbic system (especially hippocampal formation). They conclude that brain stem mechanisms along with their reverberating cyclic connection with the neocortex form the basis for consciousness. Glasser (1955) emphasizes the fact that central mechanisms controlling consciousness are also involved in memory functions.

Amongst the significant developments in neurophysiology, recognition of functional importance of limbic system of the brain has now assumed particular importance. This limbic system contains the great limbic lobe of Broca with its subcortical cell stations. Important components of the limbic cortex are the orbitomesial surface of the frontal lobe, anterior cingulate

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gyrus, anterior insula, the temporal pole, the pyriform area (periamygdaloid), the hippocampal and the dentate gyri and the uncus. These regions fall within the classification of archipallium or mesopallium as differentiated from neopallium or neocortex. Subcortical cell stations of those regions are amygdaloid nuclei, hippocampus, septal nuclei, hypothalamus and thalamic nuclei and parts of the basal ganglia.

Various autonomic responses both sympathetic and parasympathetic and changes in behaviour are seen on stimulation of or ablation of different limbic structures. Bailey and Sweet (1940) demonstrated a rise in blood pressure on the stimulation of the posterior part of the orbital surface of frontal lobe. This was confirmed by various workers in animals (Delgado and Livingston, 1948; Kaada et al, 1949; Anand and Dua, 1956). Lesions produced in these frontal lobe structures revealed a very slight drop in blood pressure (Anand, Dua and Chhina 1957) with rise in the heart rate. Chapman et al (1955) reported a rise in the blood pressure on stimulation of amygdala in humans. Anand and Dua (1956) reported definite rise in blood pressure on temporal tip stimulation. These findings indicate psychosomatic approach to the question of hypertension.

Stimulation of temporal lobe structures led to inhibition of respiration (Kaada, 1949 and 1952, Turner, 1954, Anand and Dua, 1956).

Changes in the gastro-intestinal motility were also observed on stimulation of limbic structures. Eliasson (1952) elicited vigorous contraction of the stomach on stimulation of amygdala. Kaada (1951) obtained inhibition of motility on stimulation of temporal poles and pyriform cortex. Anand and Dua (1956) observed inhibition of motility on stimulation of temporal lobe structures. Sen and Anand (1957) have shown that stimulation of the preoptic region of the hypothalamus and the anteromedial group of amygdaloid nuclei produce acute haemorrhagic ulcer in gastric pouches.

The cortical representation for the sense of smell has now been established to be the pyriform and the prepyriform areas by extensive studies made by anatomists (Clark, 1947, Meyer, 1949), physiologists (Fox, 1944; Berry, 1952) and neuropsychiatrists (Penfield, 1951). Clinical observations (Penfield, 1951) and destructive lesions in animals (Ruch and Patton, 1946) suggest that taste is represented centrally in the insula.

Affective behaviour has also been studied by large number of workers by stimulation and ablation of different limbic structures. Anand and Brobeck (1952) reported that rats who became vicious after hypothalamic lesions became non-vicious after amygdaloid lesions. Ward (1948) and Gleeles et al (1950) reported that cingulate ablation produced tameness. Kennard (1955) reported that such a lesion makes cats confused and they show hypomotility. Anand, Dua and Chhina (1957) observed that restricted anterior cingulate lesion in monkeys and cats made them jealous and docile. Delgado (1955) has shown that stimulation of ventromedial quadrant of the frontal lobe and the anterior cingulate gyrus or fornix produced a ferocious male macaque completely docile and reserved form of behaviour the moment stimulation stopped. Davis (1951) concluded that hyperactivity after lesions of the orbital surface of the frontal lobe is possibly due to involvement of the head of the caudate nucleus. The same was confirmed by Anand, Dua and Chhina (1957).

As a result of extensive studies, the limbic system has been suggested to be concerned with emotional experiences and neocortex with intellectual functions. Recent studies in neurophysiology have aimed at correct orientation of intellectual, emotional and visceral control in forebrain mechanisms. These physiological investigations have led to new techniques in neurosurgery. Lobotomy or lobectomy operations are now selective and not radical depending on psychic disturbances.

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## NEURO-RADIOLOGY—See CENTRAL NERVOUS SYSTEM, RADIOLOGICAL ASPECTS OF

### NEWBORN, DISORDERS AFFECTING THE

N. Subhadra Devi

The great advances of the past two decades have had their impact on problems of the newborn. Infections have been controlled. Much has been achieved in preventing severe toxæmia of pregnancy by meticulous antenatal care. Difficult labours have been eliminated by generous use of caesarean section and low forceps deliveries and better methods of analgesia and anaesthesia. However, much remains to be learnt regarding the pathology of the early ovum, of antepartum death of the foetus, of factors which predispose to prematurity, which is the most vital problem of the day. The influence of maternal nutrition and endocrine status, on the foetus and its physiology, is also not properly known.

The concept of an abortion is changing. The definition of live birth as adopted by the World Health Organisation, National Office of Vital Statistics, is, "Live birth is the complete expulsion or extraction from the mother of a product of conception, irrespective of the duration of pregnancy, which after such separation, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movements of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached, each product of such a birth is considered live born" (Greenhill)<sup>18</sup>.

Foetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy ; the death is indicated by the fact that after such separation, the foetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles. With these newer definitions many of our concepts on obstetrical problems like antepartum haemorrhage, still-birth and prematurity will have to change.

**Foetal Deformities.**—With the reduction in other causes of foetal and neonatal deaths, congenital deformities comprise a significant percentage of foetal loss. Gordon and Ingalls<sup>16</sup> wrote, "As a cause of death in the United States, the rate from congenital malformations were 12.6 per 100,000 population in 1944. The importance of this group to the public health is indicated by its rank of tenth among the principal causes of death for all age groups. They rated third for deaths among infants under one year of age, the ratio being 553.7 per 100,000 and surpassed only by prematurity and pneumonia." The influence of viral disease, toxoplasmosis, defective maternal nutrition have been studied besides primary genetic faults. Bernard Kaye,



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David Rosner and Irving Stein<sup>3</sup> studied 273 cases of congenital anomalies in infants at the Michael Reese Hospital. A possible prenatal factor, was discovered only in 90 cases. Of this, acute maternal illness (viral disease) had occurred only in 14. Mumps, measles, infectious mononucleosis, typhoid fever, infectious hepatitis, and in short any high febrile illness, in early pregnancy, can cause developmental defects. 340 cases of viral disease in pregnancy revealed 16.5 per cent anomalies after mumps, 15.9 per cent after measles, 11.5 per cent after varicella, 5.9 per cent after poliomyelitis, 33.2 per cent after infectious hepatitis, a total incidence of 14.1 per cent. Abortions were highest after poliomyelitis and infectious hepatitis. Viral disease other than rubella accounted for 20.9 per cent of anomalies and rubella for 40 per cent of anomalies. They concluded that a history of threatened abortion does not cause congenital anomalies, and that viral disease is not a significant cause of congenital defects, hence interruption of pregnancy to prevent congenital malformation is not justifiable.

Gregg showed the relation of congenital malformations to rubella in early pregnancy. Flammer showed that second month infection is most dangerous to the embryo with 84-88 per cent incidence of defects. After the third month it is 34 per cent and from the fifth month, the foetus is not endangered. Gian Tondury, quoted by Greenhill<sup>18</sup> studying 10 foetuses, 31-51 days after conception complicated by rubella found lenticular opacities, cardiac anomalies, deafness, psychomotor disturbances. Evans called attention to dental malformations. The cataract starts as a central opacity of flattened lens, tending to advance peripherally. The virus from the mother penetrates intact chorionic villi with the foetal blood stream. Only certain organs are affected like the lens, enamel organs, epithelium of the inner ear and heart. The cytoplasm of the attached cells is decomposed, vacuolar degeneration occurs with pyknosis of cellular nuclei and finally complete dissolution. The action of a virus is comparable to that of a gene.

Increasing use of radio-diagnostic and therapeutic measures may also damage the maternal and foetal gonads sufficiently to cause gene mutations.

Though animal experiments of Warkany<sup>39</sup> have shown the relation of congenital defects to faulty nutrition, especially deficiency of vitamins A, B and E, but this has not yet been proved in man.

**Determination of Sex** of foetus before birth has been made possible by the presence of a special mass of chromatin formed in somatic cells of the female. Landrum Shettler<sup>22</sup> reported that in the human female, heterochromatic portions of the two chromosomes fuse to form a mass, which is not so in the male (only 0.6 per cent). The mass is distinct from the more generalised particles of chromatin, and its nucleic acid is mainly of the desoxy-ribose type. Smears of oral mucosa show the typical chromatin body. The sex chromatin mass is present in every tissue and organ in the female and stained cells from the amniotic fluid, obtained by aspiration, will help to forecast the sex of the unborn foetus. Dewhurst<sup>10</sup> studied 20 specimens of liquor amnii and was correct in 18 instances. Aspiration of amniotic fluid in early pregnancy is dangerous, as proved by experiments in mice (Trasler<sup>34</sup> and associates).

**Prematurity.**—According to international standards, a foetus weighing 5½ lb and less (2500 grams and less) is considered premature, irrespective of the gestation period, or if the weight is not known, birth before 37 weeks of pregnancy is premature. The incidence of prematurity in Western countries varies from 5.45 per cent to 8 per cent (West, Grier and Lussky)<sup>35</sup>. In countries where the birth weight is around 6 lb, the prematurity rate is 16.6—35.1 per cent (Llewellyn Jones)<sup>35</sup>. In practice however, in the Tropics, a weight of 4½ lb or 4 lb should be the criterion for prematurity. Prematurity accounts for over 50 per cent of neonatal deaths. In the series of West, Grier and Lussky, 94 per cent of deaths had autopsy. They found birth injury responsible for 25.7 per cent, congenital anomaly for 11.9 per cent, and infections in 5.7 per cent of deaths. Greenhill<sup>17</sup> says that the exact cause of prematurity can be found in only 40 per cent of cases. The chief of these are (1) maternal diseases like pre-eclampsia, placenta praevia, abruptio placentae (2) multiple births, (3) maternal diseases which cause premature labour, (4) foetal monstrosities, (5) habitual abortion. Prematurity is responsible for 50 per cent of neonatal deaths. Cerebral haemorrhage is extremely common. Increased incidence of breech adds to the death rate.

Prevention of prematurity is more important than the treatment of premature babies. Early and intensive conservative treatment of toxæmias, expectant treatment of placenta praevia till the foetus is well viable, adequate rest for cardiac patients and women with multiple pregnancy,

treatment of maternal diseases like anaemia and gastro-intestinal infections especially in the Tropics, control of syphilis, improvement in the nutritional status of pregnant women are important preventive factors. Generous use of episiotomy and low forceps application help to reduce the risks of birth injury and anoxia. Local infiltration analgesia is best. Russel and Betts<sup>31</sup> reported a mortality rate of 11.4 per cent with conduction anaesthesia and 24 per cent with general or no anaesthesia. Shoeneck<sup>32</sup> found that 69 per cent of prematures died within 24 hours and 75 per cent of prematures died within oneweek, and thus they swell the perinatal death rate. He classified obstetric factors as primarily responsible if the birth weight is 3 lb 8 oz or less or if a major obstetric complication or major congenital abnormality is present. Paediatric aspects are given primary responsibility if the weight is over 3 lb 8 oz and the foetus and pregnancy are otherwise normal. Obstetric factors caused 85 per cent of premature deaths, and paediatric factors 15 per cent.

*Treatment of Prematurity:* The care of the premature has seen remarkable improvement in recent years. The establishment of special premature units in institutions and provision of similar domiciliary care were first started in Birmingham (Crosse)<sup>6</sup>. The present day trend is to have special units attached to maternity wards. Crosse recommends that all babies under 4 lb should be transferred to special units in addition to those which are sick and weakly among bigger babies. Special transport facilities are available in many Western countries.

Experience in the Tropics with premature babies has shown (Devi<sup>12</sup>, Lwellyn Jones<sup>20</sup>) that elaborate arrangements are not necessary owing to the higher temperature and humidity conditions here.

The essentials of nursing care of a premature baby consist of : (1) Immediate careful resuscitation, (2) reduction of handling to a minimum, (3) prevention and treatment of infections with prophylactic wide spectrum antibiotics, (4) maintenance of body heat, (5) administration of oxygen, (6) management of feeding and (7) treatment of complications. Incubators are generally useful but not necessary except for very feeble or cyanosed babies. They may be of the closed or open type. The room temperature should be 70-75° F and humidity 60-65 per cent. In the Tropics, warming arrangements are rarely called for, but cooling arrangements are necessary in hot weather.

Breast milk is the best food (Crosse) though the protein and mineral content is too low for growth of premature babies. A milk bank is an asset to an institution. 24 hours after birth the baby may be put to the breast or bottle if it can suck, or fed with a pipette if it can swallow. If it cannot do either, tube feeding is advisable (Kuntz)<sup>21</sup>. A sterile paraffinised polythene tube, size 2, bore 1 mm, wall 0.25 mm is passed into the stomach and its outer end strapped to the cheeks. Feeding is done through a blunted needle passed into the outer end of the tube. Small feeds equivalent to one-fifth of the body weight are given at first, and gradually built up in 2-3 weeks' time. Overfeeding is a much greater danger than underfeeding owing to cardiac and respiratory complications. The complications of prematurity are *atelectasis*, *hyaline membranes*, *pulmonary haemorrhage*, *retrolental fibroplasia* and *kernicterus*.

The most common cause of death in prematures is inadequate pulmonary ventilation. Atelectasis is due to feeble respiratory movements. According to Landing hyaline membranes are formed by inhalation of amniotic fluid, concentration of proteins and compression of this concentrated protein about the periphery of the bronchioles, alveolar ducts and alveoli. Respiration must occur at least for an hour. Arey said it is due to blood proteins. Treatment consists in oxygen therapy, prophylactic antibiotics and avoidance of bronchoscopy procedures. Oxygen mist has been favourably reported on by Hardy. *Retrolental fibroplasia* is a disease of retina and vitreous seen in premature babies exposed to high oxygen tension. Vascular dilatation and tortuosity appear later, resulting in disorganisation of the lens and blindness. No remedy is yet known for this condition, but there is spontaneous resolution in many cases.

**Foetal Anoxia and Asphyxia Neonatorum.**—According to Eastman<sup>13</sup>, oxygen levels in the foetus *in utero* are equivalent to those at 3/4 mile above the Everest. At this low pressure, equal to 40 mm Hg, an adult would perish in a few minutes. The foetus manages to live and grow in this environment by several adaptations including a pronounced increase of red corpuscles and haemoglobin and increased bone marrow activity. Foetal haemoglobin has a special property of giving off oxygen more readily than adult haemoglobin. Foetal haemoglobin is almost completely replaced by adult haemoglobin five months after birth and

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is 80 per cent at birth. Because of this, the foetus is continually in a state of cyanosis and it can quickly die of anoxia. Uterine contractions, placental pathology, oxytocic drugs and maternal conditions which in themselves produce anoxia, cause foetal anoxia, which is the commonest cause of foetal death *in utero* and in the early neonatal period. Anoxia may not only cause death but cerebral palsy may also occur as a remote effect. About 50 per cent of a group of children with cerebral palsy whose record at birth was studied gave evidence of intrauterine damage at birth such as irregular or repeated vaginal bleeding in the mother, prematurity, prolonged second stage of labour, and a "poor" birth condition. Retrolental fibroplasia is one of the commonest causes of blindness in children and is due to a response of immature neural tissue to anoxia. The anoxia may exist primarily because of inadequate oxygenation of the blood or be induced by exposing a premature to an environment of high oxygen concentration.

Richard de Soldenhoff and Gordon Brill (1954)<sup>30</sup> studied 50 avoidable still births and neonatal deaths with signs of foetal distress in 38 cases, in 1950-1951 and a further 50 cases of foetal distress. They found that in prolonged labour alone, mild foetal distress occurred, that in cord compression, distress was severe and unrelated to uterine contractions and that in pelvic contraction, slowing of the heart occurs during contraction and regains after contraction. The general conception of a prolonged labour as one lasting 48 hours should be changed to 24 hours preferably, considering the dangers of prolonged labour to the foetus. All signs of foetal distress should be heeded as indicating mild or severe distress with attendant dangers, "immediate and remote".

The prevention and treatment of the syndrome of asphyxia neonatorum was studied by Little (Jr.), Hampton and White<sup>9</sup>. They do not believe that the problem of asphyxia neonatorum is mere exercise in resuscitation. Neurologic damage is a great danger, but preventable antepartum and intrapartum conditions, the age of the mother if over 40 years, primigravidae, cardiac disease and failure, anaemia, pulmonary disease, infections, genito-urinary and gastro-intestinal diseases, metabolic diseases and toxae-mias all increase the incidence of asphyxia.

Faults in the products of conception, viability of germplasm, foetal disease and congenital anomalies, induction of labour with drugs, complications of labour and type of delivery, analgesics and anaesthetics, are fundamental causative factors.

The ultimate residual lesions of antenatal and neonatal asphyxia were studied by post-mortem examination on mentally deficient, spastic or epileptic children—definite focal cortical necrosis, nodular atrophy of the cerebral cortex, focal and diffuse alterations of the corpus striatum, areas of cortical and subcortical softening incident to arterial occlusion, demyelination of the cerebrum and central cyst formation were found. There is much evidence that some of the degenerating brain diseases of infancy and childhood are anoxial. Experimentally similar lesions were obtained in animals. Witterdal<sup>36</sup> followed 536 babies after forceps for 12 years (317 were examined). In 21, there was mental retardation, and 15 had physical defects, whereas in 2000 children after spontaneous delivery, there was no difference in mental or physical health. Greenhill<sup>17</sup> says, "I believe that anoxia or asphyxia neonatorum sometimes leaves permanent sequelae in babies who do not die shortly after birth. The same is true of cerebral haemorrhage which results from trauma or anoxia".

Fitzgerald and Macfarlane<sup>15</sup> analysed 205 cases of foetal distress and intrapartum foetal deaths in 3618 deliveries and found that foetal distress was present in 8 per cent of mothers over 30 years, whereas it was found in 6.5 per cent of mothers under 30 years. Primigravidae were 8.9 per cent and multiparae 4.6 per cent, 13.1 per cent in antepartum haemorrhage and 6.1 per cent in normal cases. Where the foetus was postmature 14 days, it was 13.4 per cent and in prematurity of 14 days, it was 8.4 per cent. When meconium staining was noted it was 44 per cent, with frank meconium 69 per cent and with alterations of foetal heart, it varied from 59-62 per cent.

Postmaturity has been shown to be a predisposing cause of foetal anoxia. Walker<sup>37</sup> comparing the oxygen saturation of cord blood of babies born by caesarean section and vaginally at different periods of pregnancy found that at 30 weeks, there is 70 per cent saturation, at 40 weeks, 60 per cent but that at 43 weeks it was 30 per cent which is the level in a foetus in severe distress. The critical point is the forty-third week when partial impermeability of the placenta occurs. Toxaemia and diabetes act on placental permeability like postmaturity.

To this anoxia, the foetus may react in various ways. (1) by building more haemoglobin, (2) premature respirations *in utero* leading to considerable aspiration of liquor amnii, (3) progressive anoxia leads to rupture of small cerebral vessels. James Walker<sup>38</sup> induces labour after 40 weeks in cases of pre-eclampsia and in cases of early threatened abortion history. If foetal distress develops, he recommends caesarean section. Particularly in primigravidae over 25 years, he induces labour at 40 weeks and if the hind water tap reveals meconium staining he proceeds with a caesarean section. He allows spontaneous delivery if she is under 25 years.

Louis Resnick<sup>24</sup> compared foetal mortality in relation to meconium staining. In 167 forceps deliveries with foetal distress, 28 babies were lost and with 30 caesarian sections with foetal distress, 5 babies were lost. Death was due to asphyxia in 45.5 per cent, bronchopneumonia in 33.3 per cent, intracranial damage in 18.1 per cent and other causes in 3.2 per cent. This high mortality could be reduced by expert supervision during labour, expert paediatric attention and particularly in the presence of postmaturity.

**Resuscitation of the Newborn.**—Considering the aetiology and pathology of asphyxia, resuscitation measures resolve into the following: (1) Maintenance of patent airway by tracheal intubation or laryngoscope, (2) 15-30 per cent Trendelenburgh position to facilitate drainage, (3) warmth and gentle handling to prevent further shock, (4) intragastric oxygen by double catheters inserted into the stomach (Akerren and Furstenberg)<sup>1</sup>, (5) preliminary gastric aspiration of stomach contents to prevent regurgitation and choking later and (6) analeptic drugs like coramine, alpha lobeline, etc., cause mild but fleeting stimulation only, and can be potent convulsive agents. If convulsions occur, the little but precious oxygen available may be utilised and the life of the foetus be jeopardised. Nalorphine however is useful where anoxia is due to depression of respiratory centre by the morphia group of drugs and can be given to the baby, 2 mg into the umbilical vein or 10 mg may be given intravenously to the mother 10 minutes before delivery. (7) Various methods of oxygen therapy under pressure: more babies are saved by timely low forceps delivery and caesarean section, which have reduced foetal deaths due to anoxia. Every labour room must be adequately equipped for treatment of foetal anoxia.

**Perinatal and Neonatal Mortality.**—By perinatal mortality is meant late still birth and first week neonatal deaths. These two are grouped together as *obstetric deaths* as they are mainly due to obstetric complications for which the obstetrician is directly responsible.

According to Edwin Gold<sup>14</sup> early neonatal deaths comprise 90 per cent of neonatal deaths and 90 per cent of these are due to perinatal causes like prematurity (51 per cent), birth injuries (15 per cent), anoxia and erythroblastosis (11 per cent). Late foetal deaths (after 28 weeks) comprise 50 per cent of perinatal mortality. Of these 20.4 per cent are due to maternal conditions like toxæmia, abnormal labour and chronic diseases, 38 per cent due to conditions in the foetus, placenta and cord, and 41.6 per cent due to ill-defined or unknown causes. He suggests that much information of a preventive and therapeutic nature can come from autopsies on foetal deaths and the development of a perinatal conference with the obstetrician, paediatrician and anaesthetist and pathologist.

Evidence from Aberdeen on the causes and prevention of first week deaths by Baird, Thomson and Duncan<sup>2</sup> as gleaned from clinical records showed that still births could be classed into seven cause groups: (1) Mature—cause of death unknown, (2) premature—cause of death unknown, (3) birth trauma, (4) pre-eclampsia with or without antepartum haemorrhage, (5) foetal deformity, (6) haemorrhage (placenta praevia and accidental haemorrhage without toxæmia), and (7) all other causes.

Prevention consists in improving the level of health of mothers and their nutrition, provision of the highest standards of hospital care in all "high risk" cases, reduction of proportion of multiparae in whom there is a high perinatal mortality than in younger groups, by proper contraceptive advice and sterilisation methods.

Perinatal mortality is as high after caesarean section as the overall perinatal loss in all types of deliveries according to Donald McNeill<sup>11</sup>. Among 35,890 deliveries at the Buffalo General Hospital, the perinatal mortality rate was 3.04 per cent. Among 944 caesarean sections, it was 6.3 per cent and corrected rate was 4.09 per cent. The higher rate for caesarean section is due to greater anoxia, and premature babies in the group. Caesarean section is no good for premature babies and should be avoided.

A five year survey of neonatal deaths by Schnutz, Smith and Foley<sup>33</sup> have shown a rate of 10.48 per cent per 1000 deliveries, excluding foetuses under 1000 grams and monsters.

## Newborn, Disorders Affecting the

He concluded that: (1) Prematurity is by far the major cause of neonatal deaths, (2) prognosis is directly proportional to the weight of infant, (3) chances of survival increase, the longer the child lives, (4) neonatal deaths are six times greater in breech, caesarean sections and midforceps and ten times greater with version and extraction, (5) pre-eclampsia increases mortality slightly but much less than formerly, (6) prolonged labours are associated with three and half times greater mortality, (7) *abruptio placentae* and *placenta praevia* have ten times greater mortality and (8) there is eight times greater mortality in multiple pregnancies. 84 per cent of deaths are due to birth injuries or anoxia and 81 per cent come under prematurity, birth injuries and infections.

**Conditions Requiring Early Surgical Intervention.**—Recent advances in surgical technique and a better knowledge of the physiology of the new born and careful examination of the new born have made possible correction of certain urgent congenital malformations like oesophageal atresia, intestinal obstruction, congenital diaphragmatic hernia, imperforate anus, exomphalos, meningocele, etc. Careful examination of the new born especially for vomiting, cyanosis, intestinal obstruction are very necessary for the early detection of these lesions. Adequate radiodiagnostic methods help in their detection. Surgery offers the only chance of survival though not a very promising one.

**Erythroblastosis Foetalis and Kernicterus.**—At the Seventh M. and R. Paediatric Research Conference<sup>28</sup>, Potter reported an incidence of erythroblastosis foetalis of one in 641 children among all births; among multigravidae, one in 395, and among Rhesus negative multigravidae one in 59 cases and among still births one in 9. Though figures are not available for the Eastern countries, the condition is far less common here. Exchange transfusion gives best results—13 per cent deaths according to Molleson while 37 per cent with simple transfusion. Kernicterus though associated with erythroblastosis and due to late staining of the basal ganglia can also occur without the condition, particularly in premature babies and is then said to be due to anoxia (Govan and Scott)<sup>20</sup>. ACTH and cortisone, have been tried, in prevention of complications of erythroblastosis but without definite results (Maurice Mayer and Paul Ducas)<sup>29</sup>.

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## NIGHT SOIL, DISPOSAL OF

A. K. Niyogi

The problem of disposal of night soil is a very serious one in India particularly owing to poverty and ignorance, yet, unless proper methods for this purpose are adopted by the people, most of the food and water-borne diseases will continue with their present day severity. Chatterjee<sup>1</sup> describes a new type of well latrine. Its mouth is covered with split bamboo mattress and earth, and is fitted with a ventilation pipe. The pan and the water seal are outside and are connected to the well by an oblique pipe. He found this type satisfactory for non-rocky areas of West Bengal but pleaded for improvements particularly of the water seal, which catches faeces if made of cement concrete and which is too costly if it is of glazed earthenware type. He recommended more health propaganda and free supply of squatting plates with pan and water seal for rapid progress of the scheme of sanitary improvement. It is interesting to note the effect of economic factor on the progress in latrine construction in the villages where he worked. The author reported that 17.5 per cent of the 200,000 houses have now provided themselves with latrines with free supply of concrete squatting plate and with water seal (cost, about rupees ten). In a comparable community development project, viz. the National Extension Service Area where no free supply was made the percentage was only 2 per cent.

The problem of disposal of sewage is also a serious problem in many cities. Although the sewage is changed from the night soil stage, the microbiological character of the former is still a very serious menace to health.

Bhaskaran et al<sup>2</sup> in their experiments found that helminth ova survive digestion of sludge for 120 days at normal air temperature. Drying the sludge is not effective in killing the ova unless very low level of moisture is attained which is not practical. If the sludge is heated to 135° F for one hour, all the ova are destroyed.

It has been seen that 50 per cent removal of helminth ova occurs by sedimentation of sewage for about 2 hours. Over 95 per cent but not 100 per cent removal occurred by activated sludge treatment and trickling filter or by septic tank with contact bed in spite of both being followed by chlorination of the effluents.

Thus none of the sewage treatment methods leads to complete elimination of helminth ova from the effluents or the sludge.

This raises the question of public health risk involved in the use of sewage effluents or sludge in agriculture and other methods of disposal. Fruits and vegetables taken raw should not be grown on such irrigated or manured land. If the effluents are to be let into the rivers at least chlorination of the effluents must be resorted to.

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## NOSE AND NASAL ACCESSORY SINUSES, DISEASES OF

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**Epistaxis.**—This is of frequent occurrence in the practice of otolaryngology. Many a time arrest of bleeding is a relatively simple matter and can be managed by local therapy. At other times it creates a problem demanding serious consideration. Stewart and Sammon<sup>15</sup> report with encouraging results, the use of deep X-ray therapy in severe progressive epistaxis. The

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nose is packed in the usual manner and five daily treatments are given. The maximum dose varies from 2000 to 2500 r. Histological examination of the nasal mucosa after the treatment showed intimal thickening with consequent narrowing of the lumen of the blood vessels.

Peele<sup>11</sup> reports with great satisfaction the use of Adrenosem in the control of haemorrhage from the nose and throat. Adrenosem is a synthetic chemical. It is an oxidation product of epinephrine which is prepared as a stable aqueous solution by using sodium salicylate as solvent. It is suitable for oral or parenteral administration. Adrenosem has no sympathomimetic action, nor has it any effect on blood clotting mechanism. It checks bleeding by causing a correction of excessive permeability, and an increase in capillary resistance. It has no effect on large severed blood vessels or arterioles. Adrenosem has a very high index of therapeutic safety and at recommended dosage levels there are no contra-indications. In rhinology it will be very useful in the control of spontaneous epistaxis and in controlling bleeding from the nose at the time of operations and post-operatively after removal of the nasal packing.

These procedures which facilitate the control of haemorrhage appear to be a welcome addition to our therapeutic armamentarium.

**Deformities of the Septum.**—Various operative procedures have been described to correct septal deviations and the nasal deviations often associated with them. No one procedure is applicable to all types of cases. Goldman<sup>3</sup> describes a technique which he believes to have the following advantages :

(1) Restoration of septal function, (2) prevention of saddling deformity, (3) prevention of nasal tip drooping, (4) prevention of flaccidity of septum by retaining semirigid structures anteriorly and rigid or bony structures posteriorly, (5) prevention of retraction by retaining or regaining a straight septum, membranous septum, and columella, (6) lessened vulnerability to subsequent trauma, and (7) obviated need of free grafts for replacement camouflage or support.

The procedure is based on the principle of mobilisation of the caudal end of the septum to the middle line by utilising pedicle flaps of the caudal deflections and central replacement of the deviated posterior osseocartilaginous parts.

**Allergy.**—The therapeutic use of ACTH, cortisone and subsequently that of the synthetic steroid prednisone in a wide variety of conditions referred to as collagen diseases, has opened up a new method of treating conditions in which allergy appears to be an aetiological factor. The exact mechanism of action of these drugs in the allergies is not definitely known. They probably act by neutralising the enzyme hyaluronidase which is liberated when an allergic reaction takes place. Allergic oedema is thereby prevented. They also suppress the resistance mechanism by which the body meets invasion by pathogenic bacteria or other irritants. The dosage of these drugs is still not standardised. An attempt should be made in each case to determine the least amount capable of maintaining clinical improvement. These drugs show a remarkable capability of suppressing the symptoms of vasomotor rhinitis and nasal allergy though recurrence of symptoms often occurs after the cessation of treatment. Shrinkage and improvement of the colour of the mucous membrane are the most significant changes noted after treatment with these drugs. Polypi also show shrinkage and sometimes entirely disappear. Secretions tend to disappear first. Often the sense of smell returns within a few days of starting the treatment. Symptomatic relief can also be obtained by the topical administration of cortisone. No untoward general or local effects have been noted and so this appears to be a very promising method of avoiding the undesirable effects of these drugs. There appears to be ample justification to use these drugs in patients not benefited by the conventional methods of treatment. These drugs have also been found to be very useful in the treatment of lethal granulomatous ulceration of the midline of the face. The clinical picture of the condition is one of progressive destruction of the nose, face and pharynx with complete lack of resistance on the part of the patient to the progress of the disease. The aetiology of the condition is still not known. Histologically the appearance of the lesion suggested Hoover Arthus phenomenon. Formerly many remedies were tried but the condition often resulted in a fatal outcome in spite of what was done to the patient. On the assumption that the condition is essentially allergic in nature, these drugs have been tried by many and they seem to produce a healing tendency and so offer the only hope of saving the patient's life in this lethal disease.

Van Alyea<sup>19</sup> in a paper on allergic sinusitis states that the successful management of allergic sinusitis is contingent upon control of allergy. Nasal and sinus allergy is in reality a catarrhal inflammation characterised by tissue oedema with eosinophilic infiltration and a mucoserous



discharge of glandular and goblet cell origin. When this occurs completely, it leads to formation of polypi. These commonly arise from the margins of the sinus ostia, the crest of the uncinate process and the anterior face of bulla ethmoidalis. They do not originate from within the ethmoidal cells as it is generally believed and so these cells should be left intact in the operation of polypectomy.

The usual symptoms of nasal allergy are present but they become more pronounced with the onset of superimposed sinusitis. The diagnosis is made on the history, the character of the nasal mucosa, the presence of pus and polypi and the result of nasal smears and skin tests. Radiographic examination shows mucosal thickening and the presence of polypi. Examination of the exudate from the sinuses is helpful in the diagnosis. A pale exudate containing a preponderance of eosinophils is indicative of a non-purulent allergic sinusitis, a yellowish mucopurulent discharge contains many neutrophils and is characteristic of an acute purulent attack, while the exudate of greyish or greenish colour with a preponderance of lymphocytes and plasma cells denotes chronicity. Exudate with a foul odour is often found in a completely blocked sinus or it may be classified roughly into five groups. These include cases of acute suppurative sinusitis on an allergic basis; those with structural defects and polypi blocking sinus drainage; those with chronic oedema constricting the ostia; and the cases of chronic sinusitis with or without polyposis, which have been subjected to one or more radical surgical procedures. Apart from the allergic management, treatment of allergic sinusitis consists in the establishment of adequate drainage. Radical surgical procedures are not indicated in these cases.

**Atrophic Rhinitis.**—In the past various surgical procedures have been devised to narrow the nasal cavities in atrophic rhinitis. This was achieved by inward displacement of the lateral nasal wall or by implanting autogenous or heterogenous material beneath the mucoperichondrium and mucoperiosteum of the septum. Seltzer<sup>13</sup> reports the submucous implantation of Ivalon, a polyvinyl sponge, with excellent results. This sponge is an artificial product and is prepared from vinyl alcohol by an aerating method that creates a finely porous foam-like structure. In this state it is fixed in formaldehyde to make the foam structure permanent. It has been found inert, producing a minimum reaction or none at all. The sponge becomes organised by ingrowth of connective tissue and blood vessels, and in the cases reported has given unusual satisfaction as compared with the other materials used for similar purposes. The patient is prepared as for any intranasal operation and under local anaesthesia, the mucosa over the atrophic turbinates is undermined. A piece of sponge, shaped both in outline and size to produce the desired restoration, is inserted into the submucous pocket. Pieces of sponge should also be introduced submucously into the septum and over the floor, when the nasal cavity is unusually roomy. This operation can also be utilised in all conditions where the nasal cavity is enlarged sufficiently to disturb the normal function of the nose.

**Vasomotor Rhinitis.**—Very often no causative allergen can be discovered in perennial vasomotor rhinitis. In its absence there must be some other mechanism which produces the symptoms of nasal allergy. Sensory and autonomic innervation of the nose is very rich and it is a common clinical experience to notice changes in the nose in cases of affections of other parts of the body. Krajina<sup>8</sup> reports the results of investigation and discusses the relation between reflex reaction of the nose and other functions of the organism especially in the case of vasomotor rhinitis. It is their opinion that in the reflex of the nasal mucosa, in addition to the trigeminal as a sensory nerve, an important part is also played by the autonomic nerves, especially the sympathetic nerves. The nose receives sympathetic innervation from two areas: through the spurs of the carotid, and from the cervical sympathetic ganglia through the deep petrosal nerve. The sympathetic nerve can cause under-reflective visceral reflexes, and through the connection with the posterior roots of the sensory nerves somatic reflexes as well. Derangements of the skin, endocrine glands, blood and tissue can provoke strong reflex reactions in the nasal mucosa in predisposed individuals, liberating H-substance which leads to local disorders and the appearance of the symptoms of nasal catarrh. The patients themselves sometimes declare that exhaustion, excitement, etc., can cause nose troubles. All these harmful agents are actually stresses, which owing to hyper-reflection, can lead to disorders in the organs and places with high innervation. In the nose local mechanisms also play an important part. For the production of vasomotor rhinitis three facts are then necessary; they are stress, hyper-reflection and an area with a rich but functionally unbalanced neuromuscular apparatus. The reason for hyper-reflection is the altered relation between hyaluronic acid and the ferment hyaluronidase.



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To show that the nervous component of hyper-reflection of the area of the nasal mucosa plays an important part in vasomotor rhinitis, and to prove the correctness of their attitude, they injected novocaine locally with relief of symptoms to some extent in a few cases.

**Sinusitis.**—Treatment of infections of the nasal accessory sinuses has undergone a remarkable change during recent years. This is due to such facts as understanding the physiology of the nose, the role played by allergy in the aetiology and the introduction of antibiotics, antihistamines and related drugs. Prigal<sup>12</sup> on the basis of bacteriologic and epidemiologic investigations states that haemolytic staphylococcus is a frequent offender in the sinorespiratory infections and the respiratory flora remain relatively stable despite the use of antibiotics. Resistance to single antibiotics is readily developed by this organism, less so by other organisms. Antibiotics lose their efficiency from year to year and combination of antibiotics is superior to single antibiotics. Chronic and recurrent infections depend upon the nature of infecting organism, the host immune reactions and contact with carriers. Likewise reinfection might occur from contact with carriers within the household. Also infection becomes chronic or recurrent because of neglect of infection in other sites of the body like the eye, skin and ear. Therapy of chronic or recurrent sinorespiratory infection involves proper use of antibiotics, at times an allergic approach, the use of vaccines and eradication of foci of infection in the patient and in presumptive carriers.

Miller et al<sup>10</sup> have reported that streptokinase administered intramuscularly with antibacterial drugs is a valuable adjunct in the treatment of acute infections. Streptokinase removes some of the barriers which prevent the adequate delivery of antibacterial substances from the rest of the body to the infected area so that greater amounts of these drugs can go to the involved site. The intramuscular injection of streptokinase cannot be used without the concurrent administration of anti-bacterial agents, or spread of infection might be facilitated. Varidase was dissolved in physiologic saline so that the final concentration of streptokinase was 10,000 units per c.cm. 0.5 c.cm of this solution was given twice daily with the antibiotics.

In the treatment of chronic sinusitis radical surgical procedures have become less frequent. Frontal sinuses still present special problems on account of the difficulty of maintaining a patent opening between them and the nose. Although a number of methods have been suggested for reconstruction of the nasofrontal duct only a few of them have been proven to be of practical value. There is some general agreement regarding the use of a tube for this purpose and the introduction of inert materials has done a great deal to make successful reconstruction techniques possible. Vitallium and polyethylene tubes appear to be ideal for this purpose. Of these two, polyethylene tube appears to be the most suitable as it can be easily manipulated and is virtually non-irritating.

When these procedures are not satisfactory and sufficient the only method of giving complete relief to the patient is by performing an obliterative operation on the frontal sinus. Woods<sup>19</sup> describes an operation which combines complete closure of the frontal duct, and obliteration of the sinus without any deformity. It consists of complete removal of the lining membrane through the floor of the sinus followed by stripping the mucosa from the frontal duct to ensure its closure. The success of the operation depends upon the complete removal of every particle of membrane from the sinus and duct. Healing takes place by formation of granulation tissue which eventually becomes fibrous tissue or bone. Incision is made in the eyebrow and the sinus opened through the roof of the orbit.

Goodale<sup>4</sup> describes an operation which entails removal of the anterior and inferior walls of the frontal sinus, the complete removal of the entire frontal sinus mucosa, the base levelling of all frontal septa in sinus, a complete ethmoidectomy. The defect can be successfully corrected by a living bone graft.

Macbeth<sup>9</sup> describes an osteoplastic operation for chronic infections of the frontal sinus. This is a modification of the operation first described by Gibson and Walker for the removal of osteomata from the frontal sinus. As modification of this technique, he offers a method for mapping the sinuses on the skin and the bone, and the use of dental drill for cutting the bone flap. This method of mapping out the sinus consists in sticking two pieces of wire at right angles on the forehead, one on either side of the midline about one inch apart, and one inch above the nasion. Two radiographs of the frontal sinuses are taken, and one of these is dried rapidly. The film outside the margin of the frontal sinus is cut away and then the remainder of the film is placed on the patient's forehead, so that the images of the two wires coincide with the original

pieces of the wire. The asymmetry of these wires immediately indicates which way round the film should be placed on the face. An indelible pencil traced round the margin of the film shows the outer limits of the frontal sinuses.

The author reports that the results in relation with relief of symptoms and preservation of facial contour appear to be very encouraging.

Bergara and Itoiz<sup>1</sup> describe their technique which consists of making an osteoperiosteal flap in which as much as possible of the anterior wall of the sinus is included. This gives a good exposure of the sinus cavity, diverticula, anterior ethmoid and at the same time yields an excellent aesthetic result. After completely removing the lining, recrudescence is avoided by obliterating the cavity with fatty tissue taken from the abdominal wall of the patient during the same procedure or from fatty tissue bank. This method of obliteration of the cavity is according to him based on clinical studies and experiments made on frontal sinuses of dogs. Adipose tissue is well tolerated, fills the cavity and resists the infection of the neighbouring cavities. It also seems to have a beneficial action in the cure of the process.

**Effects of Smoking on Upper Respiratory Tract.**—The medical aspects of smoking have received notable attention during recent years. Wallner<sup>18</sup> in a review of the literature on the effects of smoking on the respiratory tract and on the basis of clinical experience states that tobacco smoke contains irritating substances and is irritative to the mucosa of the respiratory tract. The larynx is the commonest site in the respiratory tract to reveal changes considered due to smoking. The mouth and pharynx are less commonly affected on account of the cleansing action of saliva, food and liquids. The nose and nasopharynx rarely reveal changes. Alterations of the respiratory tract commonly attributed to smoking are (1) chronic non-specific inflammation, (2) polypoid degeneration of the vocal cords, (3) leukoplakia, and (4) carcinoma. Stopping of smoking leads to the relief of subjective symptoms, as well as, diminution of the objective evidence of disease.

**Radiological Aspects.**—Gordon<sup>5</sup> after reviewing the radiological findings in a series of fifty-five cases of various malignant tumours of the nose, accessory sinuses and nasopharynx concludes that there are no radiological features which are peculiar to malignant tumours in the region. However, if a soft tissue opacity is present which extends beyond the confines of the nasal cavity or of the accessory sinuses and is associated with evidence of bone destruction the presence of a tumour must be assumed until it is proved to be absent. Radiological examination will be more useful in the confirmation of the presence of a malignant tumour, determination of the site and extent of the tumour and the determination of the effectiveness of treatment.

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## NOSE DISEASES—See EAR, NOSE AND THROAT DISEASES

## OBSTETRICS, CHANGING TRENDS IN

K. Bhasker Rao

Anaemia<sup>1</sup> is a frequent complication of pregnancy in the tropics, the commonest type being due to iron deficiency, often associated with helminthic infestations. Intravenous iron therapy is indicated to restore the general condition to normal quickly as premature delivery is likely to occur in these women. Dimorphic anaemias are frequent in the tropics and respond to oral folic acid and parenteral iron. Intramuscular iron is less risky and gives almost the same response (Scott and Govan)<sup>2</sup>.

Cardiac surgery has also been done in pregnant women. Numerous papers have been published<sup>3</sup>, where mitral commissurotomy has been done in pregnancy in group 3 and 4 cases or where embolic phenomena are present, with improved prognosis; the patients have been successfully delivered following these operations. The operation is best done in the first trimester when the cardiac load is least, after a team consisting of obstetrician, cardiac surgeon and physician have decided on surgery.

A series of 15 consecutive patients who have undergone pregnancy following major thoracic surgery for tuberculosis has also been reported showing that there is no contra-indication for pregnancy in such women (Murdoch)<sup>5</sup>.

In diabetes complicating pregnancy, foetal mortality rate still continues to be high, especially during the last month of pregnancy and in the neonatal period. Administration of oestrogen and progesterone in large doses to the mother has not altered the foetal prognosis. (Clayton<sup>6</sup> and M. R. C. Report<sup>7</sup>). Maternal mortality has been very much reduced and in some hospitals, no death has been reported for 2 years and only 2 deaths in 3 years with over 12,000 deliveries (Watson)<sup>8</sup>. Perinatal mortality is also lowered though the general causes are the same. Syphilis has become rare, but prematurity and toxæmia are still the leading causes, though survival rate in prematurity has improved (Potter)<sup>9</sup>. In Johns Hopkins Hospital, from 1937 to 1949, the perinatal mortality was 3.8 per cent of which the antenatal deaths were 30 per cent, intranatal 24 per cent and neonatal 46 per cent. Anoxia, birth trauma and pulmonary hyaline membrane were important causes of death (Nesbitt)<sup>10</sup>. Donald, who has made a special study of asphyxia in the newborn, observes that in 60 per cent of the premature babies death was due to respiratory disorders. In a series of 99 neonatal deaths, he found that in 42 per cent the cause was asphyxia and in 23 per cent intraventricular haemorrhage. Asphyxia was mainly due to secondary atelectasis—pulmonary hyaline membrane, which is an eosinophilic membrane plastered to the walls of alveoli producing respiratory distress and death in 2-3 days. Intraventricular haemorrhage was due to birth trauma or asphyxia. Eastman<sup>11</sup> states that in 60 per cent of children suffering from cerebral palsy, there is evidence of obstetric trauma, anoxia or prematurity, most of them may be spastic but some of them show evidence of tremors or athetosis. He makes a strong plea to prevent these complications occurring as sequelae of anoxia and birth trauma. The M. R. C.<sup>12</sup> report states that 4 per cent of the premature babies when followed for 2 months after delivery showed evidence of almost certain loss of vision. This they said has been due to continuous oxygen administration for premature babies (4 lb or less) for 5 days or more. The longer this treatment was administered, the greater the chances are of retrolental fibroplasia, but in units where oxygen use was restricted, the survival rate of the babies did not diminish but the incidence of this retinopathy was very low.

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## OCULAR MANIFESTATIONS OF ALLERGY

T. B. Gupta

**Introduction.**: Allergy may be defined as an altered reaction capacity of the tissues, resulting from hypersensitivity to specific substances. It is not an altered reaction but a specific altered capacity to react, produced in the living organisms by exposure to living or inanimate agents. The altered reactivity is specific, because it is made manifest only when the organism is re-exposed to the same agent that produced the changed reactivity. The substances responsible for the hypersensitivity are known as antigens or allergens and they may be bacteria, or their products, or inert matter quite innocuous to the normal individual. Only a small proportion of individuals, about 1 per cent (European writers) have a tendency to allergy and become hypersensitive after exposure to allergens. In our country, the incidence varies from place to place. In damp areas, the incidence is higher and in my view, would not be less than 5 per cent.

It is now generally agreed that practically all the tissues of the eye may be sensitized and may become the sites of allergic reactions. Sensitization may occur either primarily or as a part of a general process. Primary sensitization is produced either by absorption of airborne allergens from the conjunctival sac, of bacterial products from a focus of infection within the eye, or of the organ-specific tissues of the eye, lens protein or uveal pigment, which under certain circumstances, may act as foreign proteins. In such cases the portion of the eye, the conjunctiva or the uvea where absorption takes place, is specially sensitized, and systemic sensitization is secondary. Sensitization of the eye as part of a general process results from allergens, usually bacteria or their products, carried by the blood or the lymph, and affects primarily the vascular tissues of the eye, the uveal tract. The subsequent allergic reaction therefore, may affect either the superficial or the deep structures of the eye and be manifested as a form of conjunctivitis, keratitis or uveitis.

I propose to mention some of the important ocular allergic manifestations structure-wise.

**Eye Lids**: The skin of the lids share many of the changes which are found in the skin of the body elsewhere when an allergic reaction occurs. Notable among such manifestations are urticaria of the lids, angioneurotic oedema, contact dermatitis, eczema and marginal blepharitis.

**Conjunctiva**: Appelbaum has described four types of allergic reactions in the conjunctiva.

1. Urticarial and angioneurotic oedema: A sudden oedematous type producing a glassy oedema of the conjunctival tissues with profuse lacrimation. This is seen typically in individuals suffering from hay fever and asthma.

2. Eczematous: This type of blepharoconjunctivitis shows considerable oedema and the lids show scaling, thickening and vesiculation. This is often due to local drug sensitivity after the instillation of atropine into the conjunctival sac.

3. Chronic or recurrent irritative conjunctivitis: This type of conjunctivitis is often associated with low-grade folliculosis with acute exacerbations and with normal bacteriological findings. Allergens responsible in most cases are pollens. The patients often complain of ocular dryness and itching. Examination may or may not reveal slight congestion of the palpebral conjunctiva.

4. Vernal catarrh: The assumption that an underlying allergy is responsible for vernal catarrh is based on the following considerations:

- (a) The typical clinical picture, the recurrences and associated itching;
- (b) The climatic and seasonal incidence;
- (c) The frequent association with other allergic conditions such as asthma, hay fever, urticaria, and angioneurotic oedema;
- (d) The absence of bacteria and inclusion bodies and the presence of eosinophils in the conjunctival secretions;

## Ocular Manifestations of Allergy

- (e) The cutaneous sensitivity and the positive reaction to specific allergens, and
- (f) The favourable response to local cortisone therapy.

However, the frequent inability to demonstrate a specific allergen in many cases of vernal conjunctivitis has led to other theories, such as the association with endocrine disorders and to doubts concerning its allergic nature.

**Sclera :** Scleritis and episcleritis are now regarded as allergic manifestations to tuberculous and streptococcal toxins. Cure in several cases of episcleritis periodica fugax by avoidance of certain foods and relief of pain by the use of local antihistaminics has been claimed (Grossman and Loring).

**Cornea :** Several corneal affections have been attributed to allergy. Notable examples are phlyctenular keratitis, marginal ulcers, superficial punctate keratitis and interstitial keratitis. It has now been proved beyond doubt that phlyctenules are allergic manifestations of some internal toxæmia. The toxin responsible in majority of cases is tuberculous, streptococcal toxin being responsible in small percentage of cases. Syphilitic interstitial keratitis is also supposed to be allergic in origin because of the failure of antisyphilitic treatment to influence the course of the disease, the frequent failure to demonstrate spirochaetes in the cornea, the frequent tendency to local recurrences specially after cortisone therapy. Allergy is held responsible for some cases of clouding of corneal grafts. Thus Maumenee demonstrated that this could be produced by donor-recipient sensitization ; Castroviejo blamed bacterial allergy.

**Uveal Tract :** Allergy as the basis of uveal tract affections is seen in non-granulomatous uveitis, sympathetic ophthalmia and endophthalmitis phaco-anaphylactica. According to Allen C. Woods, the non-granulomatous uveitis is due to a bacterial hypersensitivity, as distinguished from granulomatous uveitis which is due to an actual invasion of uveal tract by the causative organisms in the living forms. The former is dependent upon a prior infection with specific bacteria. The original infection may have been in the eye or elsewhere in the body. Once this hypersensitive state has been established, an allergic inflammatory reaction may be elicited either by contact of the sensitised cells with a soluble bacterial protein or by direct contact with a living or dead bacterial body.

Allergy as the basis of sympathetic ophthalmia was suggested by Elsching in 1910. He demonstrated that uveal pigment possessed antigenic property and suggested that following injury to the eye, there was absorption of the pigment, general dissemination and production of hypersensitivity of the body as a whole, specially of the fellow eye. Woods has also supported the above view on the basis of his skin tests with uveal pigment. Although virus has been suggested as the aetiological factor in sympathetic ophthalmia by many, allergy has also not been ruled out and at present its aetiology is still unsettled.

In endophthalmitis phaco-anaphylactica the allergen responsible is lens protein. This non-infectious inflammation of the uveal tract may follow the second or the subsequent incisions of the lens, or may develop in an eye after an extra-capsular extraction where the lens cortex has been left for absorption.

**Lens :** Atopic cataract or cataract associated with neurodermatitis is an example of allergic changes in the lens.

**Retina and Optic Nerve :** Very few allergic reactions have been recorded.

**Diagnosis :** The following points are helpful :

- (1) History—family history and personal history of asthma, hayfever, eczema, etc.
- (2) Blood count for eosinophilia
- (3) Stool examination for protozoa and helminths
- (4) Conjunctival scrapings, smear examination may demonstrate eosinophils
- (5) Culture of conjunctival scrapings and secretions would be negative for any pathogenic bacteria in cases of allergic affections
- (6) Skin tests such as scratch test, patch test and intracutaneous test
- (7) Therapeutic test : Response to anti-allergic therapy may be helpful in settling the diagnosis

**Treatment :** The ideal treatment in an allergic affection is to find out the offending allergen, then either to remove it from contact with the individual suffering from the condition or to desensitize the individual to the allergen, so that hypersensitivity reaction will no longer occur. In case of inability to do either of the two, the following palliative measures should be tried.

1. Adrenaline drops in strength of 25 minims of 1 in 1000 sol. in one ounce of water or normal saline. It relieves itching, discomfort and oedema in affections of lids, conjunctiva and cornea.
2. Acetic acid drops (1 per cent) is also very helpful in controlling itching in vernal catarrh.
3. Antihistaminics : Working on the basis that anaphylactic and allergic manifestations are due to local liberation of histamine or histamine-like substances, a large number of anti-histaminics have been tried. They can be used both locally in form of drops or ointment or systemically. Antistine, Benadryl, Pyribenzamine, Dibistine, Histantin and Neoantergan are some of the drugs used widely in allergic affections.
4. Steroid therapy : In recent years, ACTH, cortisone and hydrocortisone have been used widely in allergic affections with varying degrees of success. They have proved to be excellent remedies in controlling the local symptoms and signs, but the effect is not lasting. They only modify the reaction of the tissues to the allergen—antibody combination without affecting the allergens. Reasons for this modification are not known.
5. Beta irradiation : This has been used with success in the treatment of vernal conjunctivitis. It also checks the invasion of cornea by blood vessels.

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## OESOPHAGUS, CONGENITAL ATRESIA OF

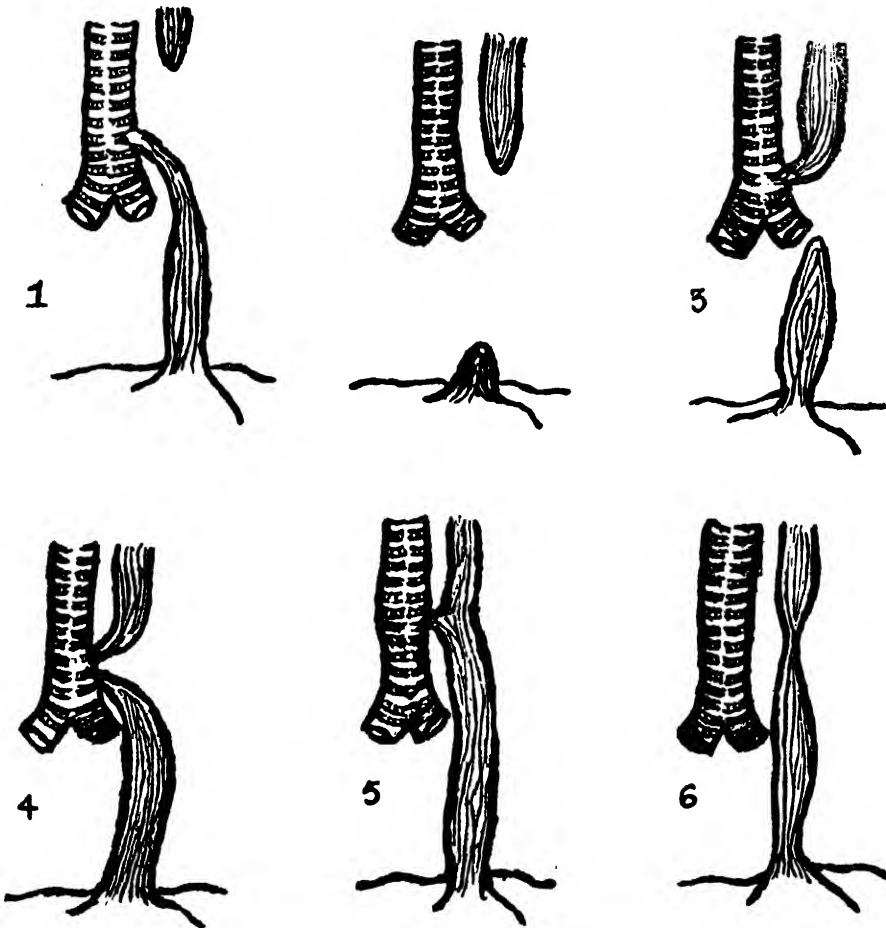
R. Mahadevan

Congenital atresia of the oesophagus is a rare type of anomaly occurring in about one in 2000 births. It is a serious condition, death occurring within a few days of birth, unless promptly diagnosed within the first few hours after birth and operated within another 24 to 36 hours. Indeed till 1939, in spite of efforts of surgeons the world over, there was not a single survivor (Gross, 1953). The first successful case was in 1939 by Ladd and at about the same time Leven also adopted a similar method of operation, independently and successfully (Gross, 1953). Far reaching advances in the method of operation have now been made and a large measure of success has been reported (Humphreys et al, 1956, Gross, 1953). The present day success is due to a combination of various masterpieces of achievement, which include improved methods of hydration of these dehydrated infants, a correct understanding of fluid and electrolyte balance, use of powerful antibiotics, improved methods of anaesthesia, and evolvement of a technique whereby the anomaly is corrected by operation at a single sitting. Success of these methods has created increasing interest in and greater awareness of the condition and naturally more common than what is now said to be 1 in 2000 live births. A number of these infants succumb without the true nature of the lesion being recognised, death being ascribed to neonatal asphyxia, atelectasis or aspiration pneumonia.

There are at least six varieties of congenital atresia of the oesophagus (Figs. 1 to 6). In the commonest type (80 to 90 per cent), the pharyngo-oesophageal pouch terminates at the second or third dorsal vertebra, corresponding to the level where the vena azygos joins the superior vena cava (i.e. 10 to 12 cm from the anterior alveolar margin) and the fundus of the pouch is 2 to 3 cm away from the vertebral column. The lower oesophageal pouch communicates with the trachea by a fistula situated 0.5 to 1 cm above the bifurcation and on the posterior tracheal wall (Ian Aird, 1957). The upper segment is dilated, hypertrophied and remarkably constant in size and shape and has a good blood supply while the lower segment is nearly always thin-walled and usually about half the calibre of the upper segment with a rather precarious blood supply (Franklin, 1948). In extreme cases there is a long segment of oesophagus missing; the pharynx ends blindly at the level of the cricoid and the oesophageal tube commences blindly just above the diaphragm. Rarely a solid cord of plain muscle joins the upper to the lower oesophageal segment; rare also is a short atresia without fistula or a tracheo-

## Oesophagus, Congenital Atresia of

oesophageal fistula without atresia. There are other associated congenital abnormalities in quite a number of these cases.



*Types of congenital abnormalities of the oesophagus.*

1. Oesophageal atresia, the lower segment communicating with the back of the trachea. Over 90 per cent of all oesophageal malformations fall into this group.
2. Oesophageal atresia. No oesophageal communication with the trachea. Under such circumstances the lower oesophageal end is apt to be quite short.
3. Oesophageal atresia, the upper segment communicating with the trachea.
4. Oesophageal atresia, both segments communicating with the trachea.
5. Oesophagus has no disruption of its continuity, but there is a tracheo-oesophageal fistula.
6. Oesophageal stenosis.

**Symptoms and Diagnosis.**—The condition can be suspected and identified during the early hours of life. The child has recurrent attacks of cyanosis which are usually severe enough to excite notice. The hungry child will easily take the breast, but swallowing is accompanied by gagging, coughing and cyanosis. This may be accompanied by complete regurgitation of the feeds. Aspiration of the nasopharynx effects an immediate improvement, but symptoms recur as soon as feeding is attempted again. Atresia is the commonest cause of persistent choking and cyanosis in the new born child and midwives and others who undertake care of the infant in the first hours of life should be taught this (Franklin, 1948). As the swallowing mechanism is blocked, saliva constantly rolls out of the mouth and should not be mistaken for the so-called "excess salivation". Attacks of cynosis may be mistakenly attributed to tentorial tears and

atelectasis, and regurgitation may be mistaken for true vomiting and a wrong diagnosis of intestinal obstruction may be made, particularly if there is bile in the vomit, as may occur in regurgitation of gastric contents through the tracheo-oesophageal fistula.

Once the condition is suspected, it can be very easily and immediately confirmed by passing through the nose, a number 10 or 12 urethral catheter. It is stopped by the obstruction and cannot be passed into the stomach. Skiagrams with contrast media are unnecessary. At any rate, barium should never be used for the purpose. It will spill over into the bronchial tree and being thick cannot be aspirated off by suction. It will cause massive atelectasis and death of the infant. Instillation of a few drops of a radio-opaque oil and aspirating it off after the skiagrams have been taken, is safer, but even this procedure is not without risk. The following method is safe and will give all relevant information. The infant is screened and a careful assessment is made of the condition of the lungs; The stomach and intestines are then examined for the presence of air. If air is present in the stomach and intestines below the oesophageal atresia, it is proof that a fistula exists between the lower segment and the trachea. The converse is usually, but not invariably true (Franklin, 1948, Humphreys, 1956). Bronchoscopic examination has been used to inspect the fistula and so confirm the diagnosis. This however is not an essential examination.

*Treatment:* The present accepted treatment is excision and closure of the fistulous track and restoration of continuity of the oesophagus at a single sitting. The years 1941 to 1945 may be considered as the period when several-staged operations were adopted with some degree of success, but soon given up as not being good enough.

Very often by the time the child is brought to the hospital, due to regurgitation of gastric contents into the bronchial tree, there is atelectasis to a greater or lesser extent. Some time must be taken to correct this and improve the condition of the infant. This may take about 12 hours usually, but may sometimes require 24 to 36 hours, even in cases where spill-over infection has been particularly heavy. The specific measures employed in pre-operative preparation of these cases are: (1) As soon as the condition is diagnosed all feeds by mouth must be stopped; (2) semi-sitting position to minimize gastric juice running up to the bronchial tree; (3) continuous oesophageal suction. A No. 8 urethral catheter with several holes cut into the lower end is threaded through the nose as far as it will go into the upper end of the oesophagus and constant suction is applied. This is better than intermittent suction at half hourly intervals as is sometimes recommended; (4) chemotherapy which practically consists of adequate doses of penicillin and streptomycin; (5) hydration of the child by administration of fluids parenterally. This is preferably done under the guidance of a paediatrician. Five to ten per cent glucose in water, plasma and serum albumin, are among the solutions used. Physiological saline is seldom used for fear of oedema. Gross recommends 10 per cent glucose in water, not exceeding 10 c.cm per pound of body weight, administered 12 hourly. As the intravenous administration will have to be continued through the operation and for several hours after, it is better to cut upon an ankle vein and introduce a cannula or preferably a narrow polythene tube, passing it well up the vein; and (6) administration of moistened oxygen, keeping the child in an oxygen tent.

*Operative Technique:* Gastrostomy alone, even as a palliative has no place in treatment as the feeds introduced will regurgitate through the fistula and flood the lungs. Operations in multiple stages brought some early successes, but their disadvantages are great and are no longer adopted. Here the fistulous track was excised and the communication with the trachea closed and the proximal oesophageal pouch was brought out as a cutaneous cervical fistula and connected to a gastrostomy. These procedures were accomplished in a week to ten days, but the real difficulty came in building up an antethoracic oesophagus which may take months and sometimes even years. This taxed the patience of all concerned. All are agreed now that the best method of treatment is excision of the fistula and restoration of the continuity of the oesophagus, all accomplished by a single-stage operation. But there are still differences of opinion regarding important details connected with the operation.

Intratracheal anaesthesia is adopted by the majority. Gross (1953), however, is strongly in favour of cyclopropane-oxygen mixture administered through a tightly-fitting face mask. Allison (1949) specifically states that no anaesthetic is required. Regarding the approach to the oesophagus almost all are agreed about a right-sided thoracotomy, but here again some are for extrapleural exposure and some for the intrapleural approach. Gross, who has a vast



## Oral Antidiabetic Drugs, Pharmacology of

experience of the problem recommends the right transpleural approach for all cases, regardless of the size of the infant, the condition of the lungs or the position of the oesophageal ends. There were 97 of his patients (up to 1953) living and in excellent condition with oesophageal anastomosis. This represented an overall recovery rate of 67 per cent. In infants weighing more than five lb and who had no other serious malformation, the recovery rate was 85 per cent. As against this are the results of Humphreys et al (1956), who adopted the right thoracotomy retropleural approach and recommended it as the procedure of choice. Twenty six of their 29 survivors were treated by retropleural anastomosis and so, they naturally consider it as the most satisfactory method.

As regards the actual anastomosis of the cut ends of the two oesophageal pouches, the blood supply to the upper end of the oesophagus is always good and for ensuring suture without tension the dissection can be carried even high into the base of the neck. The blood supply to the lower pouch however, is more precarious and it should not be liberated more than necessary. The vagi and their major branches should not be interfered with or severed, as this may result in atony and distension of the stomach and bowel. The open end of the lower oesophageal segment generally appears rather small for making an anastomosis; but by dilating it, it is possible to increase its diameter to two or three times its pre-existing size (Gross, 1953). For anastomosis, the method of union described by Haight seems to be the best. Here, the first step is to grasp *the entire thickness of the lower segment* (including muscularis and mucosa) and to join it with the mucosa of the upper segment, with a row of interrupted 00000 Deknatel silk sutures. Now *a cuff of muscularis* of the upper segment is drawn as a *sleeve* over the inner suture line, anchoring this muscular sleeve with a row of interrupted silk stitches around the entire periphery of the oesophagus. This sleeve extends down 3 to 5 mm beyond the inner layer of sutures (Gross, 1953). The area is further reinforced by stitching carefully over it a flap of mediastinal pleura.

A temporary gastrostomy (by Stamm's method) is performed immediately after completion of the thoracic procedure. Oral feeding may be started about the tenth postoperative day. If by the end of about six weeks, it is apparent that all feeds can be taken quite well by mouth, the gastrostomy tube is withdrawn and the gastric opening allowed to close spontaneously. Post-operative care includes oxygen administration, wet atmosphere, antibiotics and suction.

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## ORAL ANTIDIABETIC DRUGS, PHARMACOLOGY OF

V. Iswariah

Oral antidiabetics have been available periodically on the market, with varying claims and effects. Prior to insulin being made available in 1922, several antidiabetic agents were in use. Even after 1922, insulin was not proved to be the last word in diabetes and being a parenter. I drug, the search for oral antidiabetics continued.

*Evolution of Oral Antidiabetic Compounds:* The earliest oral antidiabetics seems to have acted psychopharmacologically, as 'tranquillizers' inhibiting adrenaline or thyroid output or the then unrecognised glucocorticoids. Such compounds may have been effective in mild diabetes acting as cerebral sedatives reinforced by the comforting presence of the doctor and his clinical care.

Later came a group of oral antidiabetics, useful perhaps in mild cases, acting presumably by controlling appetite and digestion. Some cathartics that prevented absorption of sugar from the gut had also passed off as oral antidiabetics. Then came a series of compounds from 1918 onwards with more potent properties. (It is interesting to note that most of these oral compounds hailed from Germany). This group included guanidine, galigin or isoamylenyl guanidine, synthalin or decamethylene diguanidine, etc. Guanidine as such was toxic to the central nervous system while the two others affected the liver and gastro-intestinal tract. It was feared that this group of compounds had actually damaged the liver, thereby lowering blood sugar and glycosuria. Myrtillin and synthalin had experimentally produced fatty degeneration of liver in

dogs and with the liver damage diabetic symptoms in depancreatized dogs had disappeared. (Helmut Maske, 1956.)

Indian medicine from time to time had advocated vegetable preparations like *Ewgenia gymbolina*, *Pterocarpus marsupalia*, *Gymnema sylvestra*, as oral antidiabetics. Their respective mode of action is not clear, though it is not just raising the kidney threshold for sugar, as thought. Certain other Indian medicinal preparations seem to have owed the antidiabetic effect to their opium content, though the raising of the kidney threshold to sugar by morphine is not established. Perhaps the oliguria of opium in some had given a hope.

Diabetox, a recent Indian vegetable compound said to contain 6 Indian vegetable products and a few minerals like zinc oxide, is also on the market.

It has however to be said that all the above oral antidiabetic agents did never seriously challenge the utility of insulin after its availability in 1922.

*The Sulpha Antidiabetics* : Janbon (1942)<sup>7</sup> when using a sulpha derivative p-amino benzene sulphamido isopropyl thiodiazole (IPTD) noted appreciable fall in blood sugar in his patients. This compound was not excreted as easily as other sulphas then in use. One may say that the 'martyrs' to the discovery of present day oral sulpha antidiabetics were really those patients of Janbon who suffered severe hypoglycaemic shock when IPTD was administered.

Loubatier (1944)<sup>10</sup>, experimenting with dogs noticed that many sulpha compounds when in high concentration in the blood, caused a fall in blood sugar. He had further observed that in completely depancreatized dogs, sulpha compounds did not induce fall in blood sugar, though in partially pancreatectomized dogs, there was a fall in blood sugar.

This study was closely followed by LaBarre and Reus (1947)<sup>8</sup> who observed that in alloxan induced diabetes in dogs, IPTD had reduced the blood sugar if the dose of alloxan was small, but when 100-150 mg per kilo of alloxan was given, there was no hypoglycaemic response with sulphas.

These and other allied observations gradually led to one presumption, that a small endogenous insulin or functioning pancreas was necessary for the sulphas to cause a fall in blood sugar in animals; they were not substitutes for insulin. IPTD having languished as a chemotherapeutic agent due to the serious side effect of inducing hypoglycaemia, on its ashes rose at least two important antidiabetic sulpha derivatives i. e., carbutamide (BZ 55, Invenol, Nadisan) and tolbutamide (D 860, Rastinon, Artosin, Orinase).

*Glucagon and Insulinase* : The study of the mode of action of the new oral antidiabetics has brought to light the possible existence of antagonists to insulin. Diabetics may be classified into (1) those who lack insulin and (2) and those with insulin antagonists. Both were treated with insulin, for substitution in one and mass action in the other, despite antagonists. Some evidence seems to suggest that the oral antidiabetics may act through the antagonists, though there is also some evidence in favour of a direct stimulant action on insulin production.

The two presumed antagonists are glucagon and insulinase. Glucagon, as it is obtained today, is a non-dialysable protein, inactivated by trypsin-like insulin, a polypeptide but differing from insulin in its amino acid content. The works of Long (1947)<sup>9</sup>, Thorgood and Zimmerman (1945)<sup>17</sup> and the observation that insulin prepared by some manufacturers had produced a 'paradoxic' hyperglycaemic reaction, had gradually revealed the knowledge that the pancreas secreted in addition to insulin from its beta cells, another hormone, presumably from the alpha cells called glucagon, and that insulin and glucagon had apparently opposing action on blood sugar level. Hence it is possible for some antidiabetic agents to act beneficially by depressing glucagon which tends to induce hyperglycaemia.

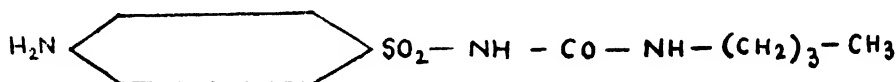
At a little later date, the observation of resistance to insulin treatment had led to the identification of insulinase. Patients with infection being generally resistant to insulin led to the hypothesis that infective organisms produced an insulinase. But Mirsky (1956)<sup>12</sup> based on his experimental study has offered a hypothesis for the existence of an insulin antagonist in the liver of rats. If there is insulinase, there is also likely to be an insulinase inhibitor in the body, on the analogy of cholinesterase and anticholinesterase.

Hence, several links in the complex mechanism of diabetes have been brought to light and the oral antidiabetic can act on one or more of these several links; indeed these links have been unearthed in the study to ascertain the mode of action of the new oral compounds.

## Oral Antidiabetic Drugs, Pharmacology of

*Carbutamide or BZ 55* : Chemists have ascertained that tertiary butyl derivatives of sulpha compounds had greater hypoglycaemic properties than methyl, ethyl, propyl or amyl compounds.

Carbutamide is sulphanilyl N<sub>2</sub>-n-butyl carbamide with a structural formula as below :



Like other sulpha compounds, it is available in 0.5 g tablets, sparingly soluble but readily absorbed from gut. Very little is acetylated in the body and the acetylated form is soluble in the urine like the sulphadimidines. The non-acetylated form is reabsorbed in the renal tubules and is retained in the body for some time. The compound is also active against streptococcus haemolyticus, staphylococcus, E. coli, the dysentery and salmonella group of organisms.

In fasting experimental animals like dogs and rabbits, doses of 0.1 to 1 g per kilo caused a fall in blood sugar in 1½ to 2 hours, the hypoglycaemia after a single dose lasting about 12-48 hours. Human beings (normal and hyperglycaemic) also showed the fall in blood sugar but with much smaller dose. In human beings, the fall in blood sugar was not often in proportion to the dose, much less was there evidence of dangerous hypoglycaemia with large doses of the compound. Clinically in diabetics, hypoglycaemic response was obtained sometimes in one day while rarely it was after 5 to 7 days. The greater the initial blood sugar level, the higher and quicker was the response, though occasionally there were exceptions. The usual dose is 2.5 g a day divided into 2 or 3 doses on the first day, followed by 1.5 g similarly divided on the second and third days followed by 1 g in two divided doses a day subsequently. Satisfactory response with a similar dosage schedule in selected elderly patients i.e., over 45, with 3 to 5 years' duration with or without insulin (though patients with less than 40 units daily insulin respond better) are recorded in India by Menon and Moses (1956)<sup>11</sup>, Patel, (1956)<sup>15</sup>, Modi (1957)<sup>13</sup>, Iswariah and Das (1957).

Bertram (1955)<sup>3</sup> is of the view that the effectiveness of carbutamide is mainly limited to subjects in whom diabetes had lasted for less than 5 to 10 years. But it is not impossible that patients with diabetes of 25 years' duration will also respond, provided some amount e.g., about 20 per cent of endogenous insulin is available. It is possible that national traits, genetic variations, dietetic habits, etc. determine the survival period of beta cells.

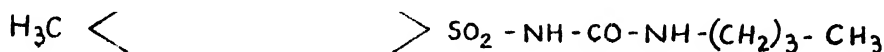
In a few cases, it was possible to suspend treatment for periods ranging from 5-10 days or even more provided the dietetic regimen was observed; but the return to drug treatment sooner or later was inevitable. In a few cases combined treatment with insulin was possible, but the insulin requirement was much less than when administered alone. In diabetic coma and in serious surgical complications insulin was imperative.

*Toxicity* : The drug has been in use for about two years and it is difficult to assess the toxic potentialities.

Hypersensitive reactions with erythematous rash and urticaria may be noticed in about 5 per cent of cases; this responds to antihistamine treatment and often the drug could be continued later. Thrombocytopenic purpura may occasionally be noticed; as the compound has to be administered for a prolonged period, blood dyscrasias are not impossible. Recently some report has been received of possible liver damage (personal communication from Eli Lilly and Co., 1956) though no report has been made to this effect in this country. But the chemist apprehending the possibility of blood dyscrasias and liver damage has been busy in providing a substitute with claim to greater safety.

*Tolbutamide or D 860* :

Here the NH<sub>2</sub> or para-amino group of carbutamide is replaced by CH<sub>3</sub> and named N (4 methylbenzene-sulphonyl) N butyl-urea with a structural formula as below :



The removal of the  $\text{NH}_2$  group is expected to reduce the toxic effects particularly on the haemopoietic system, skin and liver. Removal of the  $\text{NH}_2$  group also means removal of the chemotherapeutic properties of carbutamide, which in turn may mean prevention of deleterious action on *E. coli* and other organisms when used for a prolonged period.

Tolbutamide is also disposed of in the body by a different mechanism; there is no acetylation as with the sulphas, but the new compound is presumably oxidised to the corresponding para-carboxy acid i. e., benzoic acid which is inert.

Reports so far available in this country [Menon and Moses (1957)<sup>11</sup>; Iswariah and Das (1957)<sup>6</sup>] seem to confer a higher value to this compound compared to carbutamide.

**Mode of Action in Diabetes :** This is still speculative and no clear cut picture as to the mode of action is available. Two conferences had published their reports in 1956: one from Canadian workers (conference on carbutamide, *Canadian Med. Assoc. Journal*; Vol. 74, 1956) and a symposium on clinical and experimental effects of sulfonylureas in diabetes mellitus (Nov. 1956, "Metabolism").

The use of tolbutamide has helped to clarify one issue i.e., that the antibacterial chemotherapeutic action is not responsible for the hypoglycaemic property. It was thought that insulinase or insulin antagonist may be of bacterial origin and so the chemotherapeutic property may be of use. The specificity of insulinase has not yet been established. Mirsky (1956)<sup>12</sup> had noticed decrease of insulinase activity in the liver of some animals treated with carbutamide. Hence the first presumptive mode of action of these oral antidiabetics is by depressing hepatic insulinase or some insulin antagonist in the liver.

Some other findings (Mohinke & Biberlitz, 1956)<sup>14</sup> seem to suggest that the main action of tolbutamide is to prevent breakdown of glycogen in the liver by interfering with glucose 6-phosphatase, while carbutamide and tolbutamide both increase the glycogen of the liver. Insulin in addition is said to increase muscle glycogen.

A third possible mode of action has been suggested by Albert et al<sup>1</sup> (1956) and others<sup>4b</sup>. The oral sulpha antidiabetics are said to prevent hepatic neoglycogenesis from non-carbohydrate sources. This hypothesis may lead to the assumption that BZ 55, has a fundamental action on carbohydrate metabolism like insulin.

An earlier view with some experimental evidence has been offered by Frank and Fuchs<sup>5</sup> (1955) that the oral antidiabetics act by depressing the alpha cell activity of the pancreas and thereby glucagon.

Finally a more direct action, i.e. by stimulating insulin or potentiating insulin has been ascribed to these oral antidiabetics. Loubatier had actually obtained evidence for the liberation of insulin from the pancreas by these compounds while Ashworth and Waist (1956)<sup>2</sup> noted that large doses of invenol in rats had caused a significant increase in islet tissue and stimulated activity of the islets.

Most experiments had pointed to one consistent observation that in cases where there is absolutely no insulin available in the body (clinically juvenile diabetes) either due to complete pancreatectomy or heavy doses of alloxan, the oral antidiabetics failed to reduce blood sugar level. Wrenshall and Best (1956)<sup>18</sup> observed that it takes about 25 to 30 years of diabetes for the amount of extractable insulin in the pancreas to fall to about 15 per cent of the original; if therefore 15 per cent of normal or average insulin is still available in any pancreas, this could easily be buttressed by tolbutamide.

Best (1956)<sup>4</sup> holds that indirect action through another endocrine is not likely. The pituitary and suprarenals have not been implicated so far in the hypoglycaemic action of these compounds.

The mode of action of oral sulpha antidiabetics today is *subjudice*.

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## OTITIC VERTIGO—See VERTIGO OF OTITIC ORIGIN

### OTITIS EXTERNA, TREATMENT OF

J. V. DeSa

The cause of external otitis is obscure in most cases. Local trauma from finger nails, hair pins etc. perpetuate the irritation and establish secondary infection. The management needs modification when the local lesion is a manifestation of a general disorder such as psoriasis, seborrhoea, eczema or exfoliative dermatitis.

Acute dermatitis, which is characterized by erythema, oedema and oozing, has been reported to respond well to the following therapy : 2 per cent boric acid lotion, 1 per cent acetic acid, 1 : 1000 silver nitrate or Burrow's solution used for irrigation ; followed by topical application of 1 per cent hydrocortisone in polyethylene glycol or cortisone-polymyxin-bacitracin solution. This combination therapy has so far yielded best results in acute otitis externa.

Subacute dermatitis, generally characterized by scaling and thickening, will respond to simpler ointments such as ung. ichthammol in zinc oxide or ung. boric acid.

Chronic dermatitis, where lichenification is a feature, often proves refractory to treatment. The commonest infective organism in chronic infection is *pseudomonas* (*B. pyocyaneus*). Dossetor could demonstrate it in 50 per cent of his cases in a series of 300, whereas Radcliffe Christian could recognize its occurrence in 25 per cent of the clinically cured cases.

The cultures from the ear discharge in chronic otitis externa show a mixed flora in about 70 per cent cases. *Staphylococcus aureus* also occurs with a high incidence. Other organisms identified are *Proteus vulgaris*, *B. antitratum* and *E. coli*.

Hydrocortisone in oleaginous base or polyethylene glycol has proved encouragingly efficacious. A weekly dose of X-rays (75-100 r) may prove helpful when everything else has disappointed the physician.

Effects of topical application of oxytetracycline, polymyxin, 4-aminomethyl benzene sulphonamide hydrochloride (5 per cent), nitrofurazone, hydrocortisone, etc. were studied by Senturia et al in the treatment of acute diffuse otitis externa. None of the drugs was highly and uniformly satisfactory. When the evaluation of the drugs was done at the end of the fifth day, there was little to choose between these agents. Triphenyl methane dye was found to be bactericidal against *Staphylococcus aureus*, as well as, *Streptococcus haemolyticus*. Gram-negative bacilli were resistant to it.

Hydrocortisone acetate was found excellent in otitis externa of neurogenic type such as herpetic. It was also effective in mixed infections. Post-fenestration and post-mastoidectomy cavities that went on weeping for years and were marred by the development of granulation tissue also showed promising response to topical application of hydrocortisone ointment.

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### OTITIS MEDIA, CHRONIC ADHESIVE

J. V. DeSa

There is no general agreement on what should be included under this heading. McNaughton believes that all cases result from previous infection, whereas Cawthorne presumes that some other factors also may be responsible for this condition.

The diagnosis is established by the history of former ear trouble, conductive deafness and abnormalities but not deficiency in the drum. These abnormalities include scars, chalk deposits and impaired mobility.

## Otitis Media, Chronic, Organisms in

In all these cases both the fenestra, as well as, the incus and the head of the malleus are generally involved.

Treatment by eustachian catheterization and pneumomassage is ineffective and the results of fenestration operation are disappointing. Timely paracentesis and judicious use of antibiotics in acute otitis media will lead to success in prophylaxis.

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## OTITIS MEDIA, CHRONIC, ORGANISMS IN

J. V. DeSa

Though staphylococci, streptococci and pneumococci are the primary aetiological organisms in the middle ear infection, the flora of chronic middle ear infection shows predominance of *Pseudomona aeruginosa* (ps. pyocyanac) and *B. proteus*. They keep back the primary microbe and remain the chief agents of chronic otitis media. Treatment is disappointing because of their resistance to antibiotics and sulphonamides.

Tomic Karovic and Djorde Nemanic obtained following results on sensitivity tests in a series of 1198 cases.

	Penicillin	Streptomycin	Aureomycin	Chloro- mycetin	Terramycin	Sulpha- nilamide
<i>B. proteus</i> (514 cases) Re- sistant to .. .. .	98%	34%	80%	26%	79%	79%
<i>Ps. pyocyanac</i> (417 cases) Resistant to .. .. .	100%	25%	86%	40%	74%	69%

They tried the effect of *Lactobacillus acidophilus*, *in vitro* and *in vivo*, on these organisms. *Lactobacillus*, by virtue of the lactic acid produced during fermentation of carbohydrates in its presence, is known to displace other organisms of the intestinal flora. This knowledge helped them to study the effects of *Lactobacillus* in chronic ear infections.

A batch of patients was treated by giving them to drink half a litre of milk that was cultured with a strain of *Lactobacillus acidophilus* for 24 hours at 37°-40°C. The treatment was continued for 15 days. Another batch was treated with the same milk used locally as ear drops three times a day. Results were encouraging.

This experiment may prove a clue to the problem of infection with *B. proteus* in future.

**Pathology :** Friedmann after examining 796 bone chips removed during mastoid operations observed that sclerotic mastoid is not the cause but the result of infection. New bone formation and bone reconstruction are fundamental processes of otitis media, the end result being a sclerotic mastoid.

Failure to pneumatization makes the bone diplœtic and may become converted into compact variety when the lamellar bone gets deposited down in the narrow spaces. The resulting mastoid is clinically and radiologically sclerotic, which histopathologically is just an acellular or compact tissue. Infection can occur in any type of mastoid tissue—pneumatized, diplœtic, infantile or compact. The ultimate result is sclerosis histologically and can be distinguished accordingly.

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## OTITIS MEDIA, CHRONIC, SURGICAL MANAGEMENT OF

Mastoid operations, so far practised, have been far from satisfactory in the treatment of chronic otitis media. Dingley expressed his dissatisfaction over the radical procedures in mastoidectomy, particularly in attic disease, and pleaded for consideration of functional result in every case. Evaluating a series of 42 cases treated with radical operation, he concluded that it would be more

## Otitis Media, Chronic, Surgical Management of

reasonable to preserve as many constituents of the ossicular chain as possible to ensure some hearing for the patient. Much time did not elapse between these observations and the appearance of reports on tympanoplasty which answer all the problems in mastoid surgery. Since then the indications for mastoidectomy have become definite and may be stated as :

- (i) Frank suppurative otitis media with classical signs of post-auricular swelling and collapse of external auditory meatus.
- (ii) External and intracranial complications.
- (iii) Acute purulent otitis media which does not respond to antibiotics.

**Tympanoplasty :** Tympanoplastic procedures aim at complete eradication of the disease and reconstruction of the sound conducting apparatus.

Wullstein considers these procedures under 5 categories :

**Type I :** When the ossicles are undamaged and the tympanum can be reconstructed. The theoretical hearing loss is 0 db.

**Type II :** The lesion involves the drum and the incus. The new tympanum is directly connected to the defective ossicle by increasing the obliquity of the bridge.

**Type III :** The drum, the malleus and the incus being diseased, are removed and the new tympanic membrane is made to come in direct contact with the head of the stapes—the columella effect.

**Type IV :** The stapedial foot plate is mobile but the crura are diseased or missing. The foramen ovale is left open and the round window is given protection. The round window comes to lie in the newly constructed middle ear, constituted of the tube and the hypotympanum.

The theoretical hearing loss in II, III and IV types is only 2.5 db.

**Type V :** The stapedial foot plate is fixed and a fenestration operation is performed after clearing the middle ear. The theoretical hearing loss is 27 db.

A tympanoplasty is considered successful when the 15 db. line is reached for 500-2000 in types I-III and 30 db. for types IV-V. The average improvement should be 33.3 per cent, the post-operative air conduction level being equal to preoperative bone conduction or preoperative hearing with an aid.

The utility of these procedures is further appreciated when one observes that only about 20 per cent of the cases operated for radical mastoidectomy show a slight hearing improvement, practically none reaching a socially useful level ; the remaining 80 per cent show a post-operative drop of air conduction to 50-60 db.

**Techniques of Tympanoplasty.** —*Type I Cases:* Beales advises a myringoplasty for these cases. Wullstein criticizes this operation on the grounds that it is an incomplete operation, as one cannot adequately inspect the attic region or the tympanic cavity and that the operation will give good results for a short period only and the long term results would be disappointing because of adhesions.

**Technique of Myringoplasty:** The operation is performed under local or general anaesthesia. A modified Lempert incision is made and a small rotation flap is cut. The flap is turned upwards to clothe the upper part of the very small raw area.

A free full thickness postaural graft is cut to fit the perforation and extend on the raw area of the bone of the post-meatal wall. If the perforation is large, the graft is supported by small bits of gelatin foam placed in the tympanum.

**Tympanoplasty :** The operation can be performed by the end-aural or the post-aural route. Many surgeons prefer the post-aural route as it enables one by slight modification of the original incision to prepare the required skin graft from the site.

The attic is explored in the usual way. The bridge is thinned on the inner side to allow a space between the bony ridge and the incus. The bridge is not removed unless the disease is extensive. If the bridge is destroyed and thus requires removal, the incus and malleus must be sacrificed. The tympanum is next examined and the integrity and mobility of ossicular chain tested. Zollner advocates the use of 'schallsonade' or 'acoustic probe' at this stage. Beales deprecates this step on the grounds that it is a painful procedure and does not give much information. Granulations from the site of the oval and the round window regions are next removed. The graft is then placed in position, which should extend from the tympanic cavity anteriorly

to the antrum posteriorly. The graft is supported by small pieces of gelatin foam, if necessary. This technique is useful for type I and II cases.

If the disease is more extensive as in types III-V, the granulation tissue is removed from the oval and round window regions. The mobility of the stapes is ascertained after removal of granulation tissue. The hypotympanum is cleaned well and packed with small bits of gel-foam and a graft is placed in position in contact with the head of the stapes and supported by a BIPP packing. If the foot plate alone is left in position, the upper part of tympanic cavity is denuded of its epithelium around the oval window region to ensure that the graft will adhere at the point to produce the baffle effect.

If the foot plate alone is existing and is ankylosed as in type V cases, a fenestration operation combined with tympanoplastic procedures on the above lines is advised.

Of interest would be the work of Shuji Goto who has achieved similar results by employing slightly different procedures. In the presence of disease in the hypotympanum—once the granulations are cleaned out, a skin graft is applied without any attempt to preserve the hypotympanic air space. The skin of the bony external auditory meatus is completely removed and a radical mastoidectomy is also performed. The stapedius muscle is cut before the skin graft is applied. He prefers end-aural route in all cases. Where the hypotympanum is not involved he also prepares an air-containing space. To prevent the adhesions in this space he uses 0.2 c.cm of 1 : 500 solution of Varidase. The edges of the graft are sutured to the skin incision margins posteriorly.

**Post-operative Management:** Wullstein advocates the removal of pressure dressings on the seventh or the eighth day, however Beales leaves it undisturbed till the fourteenth day. The ear toilet is continued as usual on the following days.

**Changes in the Graft :** The graft undergoes a series of changes. The superficial epithelium disquamates leaving the surface like "raw meat" for a period of a few months. The ultimate end is a mobile, translucent, thin membrane which can be ballooned by Valsalva's manoeuvre.

Healing of the mastoid cavity is often the main problem and may take any period of time. Incomplete healing is not an uncommon occurrence.

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#### OTOSCLEROSIS

C. A. Amesur

Valsalva described ankylosis of the stapes secondary to middle ear changes (1735). Troltsch in 1881 termed the same condition as otosclerosis. Politzer in 1893 observed it to be a disease of the labyrinthine capsule. Siebmann termed it otospongiosis. Adair Dighton in 1912 showed the association of clinical otosclerosis with blue sclera and multiple fractures. This history of fractures was contradicted by Fowler in 1949.

Cawthorne<sup>2</sup> in his review of 1150 cases stated that the term otosclerosis has been applied to cases of deafness, primarily conductive and usually progressive, for which no other cause was found in the auditory or upper respiratory tracts. The classical triad of Bezold (progressive conductive deafness, with a positive family history and normal auditory apparatus) was present in many cases, though in some it was modified by underlying internal ear changes. Otosclerosis is a constitutional disease affecting otherwise healthy persons. It is the most frequently encountered cause of deafness in adults. It is bilateral and symmetrical and the hearing is neither improved, nor is the progress of the deafness arrested by any form of local treatment to the upper respiratory tract or auditory apparatus. In all but a few cases the range of hearing can be



## Otosclerosis

extended by using a hearing aid. In the large majority, clinical features are so distinctive that the diagnosis should not present any difficulty. Where otosclerosis is accompanied by some other disease of the auditory apparatus, particularly when the latter is bilateral, it may not be possible to arrive at a diagnosis. It is possible that certain forms of perceptive deafness, none of which have been included in this series, may be due to otosclerotic bone extending inwards to the spaces of the bony labyrinth.

Considerable improvement in hearing can either be obtained by fenestration, which however does not claim to cure the lesion ; or physiologically by mobilisation of the stapes, which was first attempted by Kessels in 1876, again in 1894 and was given up in 1900. The credit for the present position attained by the operation however, goes to Samuel Rosen, who first reported his successful mobilisation in 1952.

The usefulness of fenestration surgery was reported by Sourdile in 1937 and the technique was perfected by J. Lampert with a paper on end-aural anterior auricular approach to the temporal bone with a summary of 1780 cases in Arch. Otolaryngology (27 : 555, 1938). The principle of his perfected operation was (1) creation of an endosteal bone cupola on the surgical dome of the vestibule, followed by (2) circumferential incision on the base of the bony endosteal cupola, (3) eversion and removal of the intact bony cupola to uncap the perilymphatic space and expose to view the endolymphatic labyrinth. The fenestra should be about 2 mm wide and about 6 mm long, and (4) should be sealed with tympanomeatal flap.

Shambaugh George Jr.<sup>9</sup> gave the following long term results of fenestration :

1. Evidence is presented in favour of Siebmann's hypothesis that the cochlear nerve degeneration of otosclerosis is due to the diffusion of toxic products from the pathological bone when the focus reaches the endosteum of the cochlea.

2. Increased cochlear nerve degeneration does not occur in either the operated or the unoperated ear in the great majority of cases followed for 5 to 10 years. When it does occur it is more common in the unoperated ear. The reason for this is not known but Siebmann's hypothesis suggests an explanation.

3. Osteogenic closure with loss of all of the regained hearing has been a minor cause of failure in cases operated after July 1943, at the North Western University, U. S. A.

4. Partial loss of the regained hearing occurred in about one-fifth of the cases followed for five to ten years after fenestration. Some of these are believed to be due to osteogenic narrowing of the fenestra, some to post-operative hydrops, some again due to cochlear nerve degeneration, while in others no probable cause could be determined.

5. The majority (70 per cent) of fenestrated cases followed for 5 to 10 years after surgery maintained without appreciable change the level of hearing attained at one year post-operative test. It is also stated that :

- (a) Both the final level of hearing and the decibels gained are significant and important in assessing the results of fenestration surgery.

- (b) With the improved fenestration operation employed at the North Western University, approximately 75 to 80 per cent of "A" cases, 40 per cent of "B" cases, and 10 per cent of "C" cases reached the level of practical hearing at one year. In terms of decibels gained or lost, 94 per cent of "A" cases, 90 per cent of "B" cases and approximately 75 per cent of "C" cases show a significant gain at one year.

- (c) A method of objectively comparing a hearing aid with a fenestration operation is described. In the majority of cases in a small series, the hearing after operation equalled the hearing with the aid for speech reception and surpassed the aid for discrimination. A successful fenestration operation more often than not will equal or surpass an electrical aid in hearing performance. Joshi and Rege<sup>6</sup> found in a series of 307 deaf cases otosclerosis in 17.9 per cent. Out of the 14 fenestrations that they performed 12 were successful.

The success of Rosen's<sup>8</sup> operation depends on it being performed on selected cases. The level of hearing has in some been improved from the pre-operative level of 60 Db to as high as 15 Db (in illustrative cases). On an 'Atlas' audiometer, audiogram is taken before and after mobilisation. The drum is put back and sterile cotton wool is left in the ear. In some cases, neck of the stapes is left alone and the crura are amputated at the end of the foot plate by means of an operating microscope with magnification.

Success in stapedolysis surgery must be a dual concept, and must include either the achievement of the 30 Db level or the elimination of the conductive block as evidenced by an eradication of the bone air gap.

Rosen's<sup>8</sup> results of mobilisation are as follows :

1. Total reaching 30 Db or better	.. .. .	32 per cent
' A ' cases (preoperative maximum bone conduction loss 10 Db) ..	48	..
' B ' cases (preoperative maximum bone conduction loss 20 Db) ..	34	..
' C ' cases (preoperative maximum bone conduction loss 30 Db) ..	21	..
2. Hearing improved to various levels of usefulness		
10 Db or more improvement .. .. .	57	..
15 Db or more improvement .. .. .	42	..
20 Db or more improvement .. .. .	30	..
3. Improved by mobilisation at the foot plate		
(When mobilisation could not be achieved at the stapedial neck mobilisation at the foot plate at once achieved the following additional results)		
Improved to 30 Db or better .. .. .	25	..
Improved to various levels of usefulness .. .. .	55	..
4. Revisions		
Improved to various levels of usefulness .. .. .	40	..
Improved to 30 Db or better .. .. .	25	..
5. Improved following mobilisation, but later, regressed to pre-operative level .. .. .	1.7	..
6. Hearing worse than preoperative level, following mobilisation ..	1.4	..

Victor Good Hill<sup>3</sup> in his 189 cases shows 56 per cent success and 11 per cent partial gain.

Some surgeons in Europe prefer post-auricular route to the end-aural.

According to Heerman<sup>5</sup> of Germany, Rosen's mobilisation of the stapes is a gamble. If the overgrowth of the footplate is too rigid the crura break off. It is not possible to continue or to repeat the operation ; only fenestration is possible. In such cases Heermann chisels off the footplate of the stapes and establishes a pseudoarthrosis. His failures are only 5 per cent due to complete occlusion of the round window. Advantages compared with fenestration are : no vertigo, no discharge and no radical operation.

Prof. C. Satyanarayana of Madras has operated on 354 cases and recorded his results by audiometry. In a personal communication he has informed the writer that his cases would show a very large percentage of success. At Bombay, in December 1957, he demonstrated to us his modified incision. In a case where the incus was disorganised after the fenestration in the oval window, he showed good results on the table, which became less on closing the middle ear with the drum. Therefore he made a further fenestration in the drum to obtain better hearing. His detailed results will soon be published.

Agnar Hall and Curt Rytznér<sup>4</sup> of Sweden pointed out that birds required only one ossicle in the transmission mechanism of the middle ear, the columella, for adequate hearing. Bekesy<sup>1</sup> demonstrated that the effect of the ossicular chain mechanism upon the sound pressure was very small. The authors, in cases where the stapes was fractured, removed it and reintroduced the incus as a connecting link between the opening in the oval window and the tympanic membrane. The audiograms taken one year after the operation showed the reduction of the gap from 85 Db to 35 Db. Satyanarayana suggested to the authors for consideration the theoretical objection that there would be no blood supply to the transplanted part and as such it was likely to die. He offered a solution to the authors for their consideration, viz. the use of an achrylic graft instead.

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## Ovarian Contractions and their Significance in Ovulation

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## OVARIAN CONTRACTIONS AND THEIR SIGNIFICANCE IN OVULATION

A. Sitaramamurti

Attention has been recently drawn to the subject of ovarian contractions and their significance. The extrusion of the ovum is likely to be associated with the contractions exhibited by the ovaries. During the last few years, frogs have been used with increasing favour for experimental work in the diagnosis of early pregnancy. Interesting account of the contractions noticed in the ovaries of frogs and the method of recording the contractions have been described by Haranath and Murthy (1956) and an account of the histological findings which may be responsible for these contractions has been given by Haranath and Sitaramayya (1957). It has been mentioned that their attention was attracted by the rhythmic contractions exhibited by the ovaries while dissecting the locally available species of frogs (*Rana tigrina*), and the contractile structure was considered to be in the mesovarium. Rapela et al (1951) suggested that the contractions of the ovary of toad are due to the presence of myo-epithelial cells in the mesovarium, but Haranath and Sitaramayya (1957) are of the view that the contractile element is the smooth muscle in the mesovarium as detected by their histological methods. Abbot (1945) while explaining the mechanism of oviposition in *Phaenicia* (*Lucilia*) *sericate* Meig (Diptera), stated that the ovaries of this fly when excised, were still found to pulsate in the presence of nicotine, eserine and to some extent, acetyl choline and he explained that the efficient stimulus for contraction is the temperature range between 25°C and 35°C. While explaining the oviposition, it is stated that it involves a release mechanism and their attraction by light to animal matter and not the stimulus for oviposition that accounts for the deposition of eggs on meat. Pinnotti (1939) stated that contractions were observed in human ovaries as well, and in the light of these findings, it requires further experimental work and elucidation in establishing a correlation in the mechanism of ovulation with ovarian (or mesovarian) contractions.

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## OXYTOCICS

K. Bhasker Rao

*Oxytocic Drugs in Obstetrics:* Oxytocin or pitocin, now identified as a polypeptide, has been synthesised for the first time by V. du Vigneaud in 1953<sup>1</sup>. Chemically and biologically there is no difference between this product (Syntocinon) and the highly purified natural hormone. It has been now shown by the work of Bainbridge et al<sup>2</sup> that there are no qualitative or quantitative differences in the action of the natural and synthetic hormones when used on the pregnant uterus and also during labour or puerperium. This work has also been confirmed by Mayes<sup>3</sup>. But he warns that it is safe to give the drug only intramuscularly or in the form of intravenous drip. When injected intravenously in doses of 2 to 5 units, he has noted a sudden

fall of blood pressure especially in the diastolic by 15-40 mm mercury and also a disappearance or flattening of the T wave in the electrocardiogram.

Pitocin drip in uterine inertia was first advocated by Theobald in 1948. Subsequently numerous papers on the subject have been written. It is well known that it should not be used in hypertonic uterine inertia, in disproportion, malpresentations, in previous caesareans, and in multiparous women beyond the sixth pregnancy. In a recent summing up of their impressions, Theobald et al<sup>1</sup> state that the drip should ordinarily not exceed a dilution of one in 5000 and if there is no response, in cases of induction of labour, one in 2500 dilution may be tried. To be effective it should be started early in labour within 10-12 hours after rupture of membranes. Once the drip is started, the obstetrician should keep a close watch on the patient, and also on the foetal heart rate. There should not be any irregularity of the foetal heart within half an hour of starting the drip. If the response is good, the drip should be continued even to the third stage so that there may be minimal loss of blood at that time. In 3 years (1952-1954) pitocin drip was used by the authors in about 25 per cent of 1030 cases where labour was induced. All the cases except 20, were delivered vaginally. In 600 cases of inertia, one third of the patients were given the drip; of these, all but nine delivered *per via naturales*.

Noradrenaline has been shown to stimulate uterine action in labour while adrenaline inhibits it (Garrett)<sup>5</sup>. It has been claimed that dihydroergotamine is devoid of oxytocic properties and has an adrenaline blocking effect (sympatholytic effect). Topographic studies by Garrett<sup>5</sup> have disproved these claims. Dihydroergotamine has the oxytocic properties of ergot but is erratic in performance; and it does not possess any adrenaline blocking effect. Similarly it was claimed by manufacturers that some ergot alkaloids had spasmolytic effect and lost vasoconstrictor and oxytocic properties following their hydrogenation. Jeffcoate et al<sup>6</sup> and Garrett et al<sup>7</sup> have again disproved these claims. Hydergine has no spasmolytic effect and its oxytocic effect is milder than that of ergometrine and also too slow and erratic to be useful in labour.

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#### PANCREAS

B. B. Mukherji

*Insulin Zinc Suspensions in Diabetes Mellitus*: Jersild<sup>1</sup> reported the satisfactory control of 1000 diabetic patients with insulin zinc suspensions. 96 per cent of these cases were controlled on one daily injection of I.Z.S. preparations with an average dose of 40 units. In this one injection group I.Z.S. alone was given in 74 per cent, I.Z.S. plus amorphous I.Z.S. in 12 per cent and I.Z.S. plus crystalline I.Z.S. in 8 per cent of cases. Amorphous I.Z.S. or crystalline I.Z.S. alone was required in exceptional cases. Four per cent of all cases needed two injections of I.Z.S. morning and evening. Local reactions, mostly allergic in nature, were noted in only 0.8 per cent of cases and they gave rise to no therapeutic problems. The author was of the opinion that 'with preparations of I.Z.S., the results were satisfactory even in most cases where control had previously been difficult'.

Favourable results with insulin zinc suspensions in the treatment of diabetes mellitus have also been reported by Mollar<sup>2</sup>, Spencer and Morgans<sup>3</sup>, Gurling et al<sup>4</sup>, Stowers and Nabarro<sup>5</sup>, and Haunz<sup>6</sup>.

*Types of Diabetes Mellitus*: Lawrence<sup>7</sup> has classified diabetes into three following types clinically by excess or absence of body fat and by presence or absence of ketosis—(1) Lipoplethoric type—most common; no ketosis. Diabetes promptly disappears on a reducing diet without insulin. Good general health may be maintained for years without any treatment.

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(2) Insulin-deficient diabetes; causes debility and rapid wasting. It can occur at all ages but predominates in young diabetics. Its essential characteristic is ketosis. This type readily responds to insulin. Insulin treatment is essential sooner or later to re-establish and maintain a healthy life. (3) Lipotrophic diabetes—rare. Its main characteristics are general lipotrophy, intense hyperlipaemia, no ketosis, insulin resistance, hepatomegaly and raised B.M.R. General health remains good for years. All the five patients of this type were children or young adults.

Mollerstrom<sup>8</sup> classified diabetics into 3 types.—(1) Ketotic with adequate ammonia formation. These patients are not liable to coma. (2) Ketotic with inadequate ammonia formation. These patients are liable to coma. (3) Non-ketotic. Here the patients suffer from a mild form of the disease.

Hugh-Jones<sup>9</sup> studied 215 diabetic patients in Jamaica and divided them clinically into the following types: (1) Type 1—of early-age onset, insulin sensitive and ketotic (26 cases). (2) Type 2—of middle-age onset, insulin resistant, with a tendency to be obese but not to have ketosis (172 cases). (3) Type J (13 cases). It was peculiar in its onset in young thin people who were relatively insulin-resistant and lacking in ketosis. The author suggests in the addendum that type 'J' diabetes may be generally common in the Tropical countries.

Alivisatos and McCullagh<sup>10</sup> divided 172 cases of diabetes into the categories of stable and brittle diabetes. They had shown that degenerative complications were commoner in the stable group although complications were fewer in the stable group when control of diabetes had been good.

Evans et al<sup>11</sup> described 4 cases of a new type of diabetes. The patients were young, insulin sensitive and had an extreme diurnal variation of blood sugar, e.g. from an early morning blood sugar of 550 mg per cent to 50 mg per cent in the noon.

*Diabetic Glomerulosclerosis (Kimmelstiel-Wilson Syndrome):* Smith et al<sup>12</sup> studied the post-mortem histological material and clinical records from 219 diabetic subjects. Intercapillary glomerulosclerosis was present in 8 per cent of males and 21 per cent of females. The lesions were more severe in women than in men and were not found under the age of 48. In persons who died at the age of 48 or more, the incidence of this complication was found in 14 per cent of men and 31 per cent of women.

Lambie and Macfarlane<sup>13</sup> in a series of 120 post-mortems on diabetic patients found typical nodular lesions in the kidney in 46 per cent of cases. There was some evidence that poorly controlled diabetics were more liable to develop renal lesions. Of the 11 patients who had classical clinical syndrome with nephrotic oedema and albuminuria, 10 showed the characteristic kidney lesion, one had none. On the other hand, 22 cases showing characteristic lesions had no clinical evidence of renal involvement.

Reid<sup>14</sup> found in 104 cases of diabetes examined post-mortem that the incidence of nodular lesion was 25 per cent. Oedema had been noted only in 4 of these patients. Albuminuria had been present in 63 per cent (16) of these cases compared to 33 per cent of cases who had no nodular lesions.

*Hyperinsulinism and Spontaneous Hypoglycaemia:* Breidahl et al<sup>15</sup> reviewed 91 cases, the largest series of cases of hyperinsulinism ever reported. Insulin-producing islet cell tumour was found in 76 cases while 15 had no demonstrable tumour at operation or on autopsy. The authors lay down criteria for diagnosis of this condition, viz. attacks occur after fasting or vigorous physical exercise in the late afternoon or on getting up in the morning, blood sugar during the attack must be below 50 mg per cent and the attacks must be relieved by sugar. Typical attacks consist of acute mental outbursts including mania, convulsions and coma. The treatment of choice is laparotomy and pancreatic exploration. Of the 91 patients in this series, 7 died post-operatively, 59 were cured, 3 had recurrence and 22 showed persistent symptoms.

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## PANCREATITIS

K. S. Aiyer

We have been so obsessed with Lord Moynihan's picturesque description of acute haemorrhagic pancreatitis, that we do not for a moment think that lesser degrees of pancreatic pathology are either possible or do exist. Until recent years, the pathologists have also not gone deeply into this question.

The word pancreatitis covers a multitude of pathological conditions of the organ, from simple oedematous inflammation on the one hand, to acute haemorrhagic pancreatitis on the other. Most of the damage and much of the symptom-complex is due to the escape of the pancreatic enzymes from the confines of the duct system of this gland. The aetiology and pathogenesis must therefore have its secret in the process by which such an escape takes place.

It has been customary to refer to the iniquitous part played by regurgitant bile into the pancreatic duct, activating the enzymes and producing auto-digestion. The influx of bile presupposes an obstruction at the ampulla of Vater either by a stone (Opie) or by spasm (Archibald). True, bile stones have been found in about a third of the cases of pancreatitis; but it is also a fact that pancreatitis is more common in men than in women while biliary pathology is commoner in women than in men. Our own series contains only one woman with pancreatitis. Hollinshead and others, investigating the anatomy of the lower portion of the bile duct, find that the pancreatic and the bile duct open in the common ampulla of Vater in a variable proportion only; in others they open separately on the papilla or slightly away from each other. There is also considerable dispute regarding the length and width of this common channel. "Thus depending on whom one follows, one can believe that a gall stone of *exactly* the right size can cause reflux of bile into the pancreatic duct in only a tiny minority of persons or in approximately two-thirds of all persons".

In regard to the sphincteric mechanism which controls the flow of bile and pancreatic juice and therefore might be expected to cause reflux if and when it goes into spasm, here too, there is not much agreement among the anatomists. Archibald's beautiful theory has been spoilt by Mann and Giordano who point out that the sphincter in man is placed not distal to the entrance of both ducts into the ampulla, but is usually proximal to the termination of the bile duct. These authors remark rather pertinently that "Clinical imagination has preceded demonstrated facts". Another anatomical fact worth noting is that the lower portion of the bile duct undergoes a sudden narrowing of its lumen as it penetrates the musculature of the duodenum. It is much more likely, therefore, for stones to be held up here rather than in the relatively wider ampulla.

Rich and Duff have quite a different approach to this problem. They believe that trypsinogen does not require the presence of bile or intestinal contents for activation, but can cause necrosis by itself when it escapes from the ducts. The mechanism of escape of pancreatic enzymes according to them is by rupture of thinned out acini behind an obstructed duct. The intra-acinar pressure is increased usually by the stimulus of an ingested meal. The blockage in the duct is said to be due to metaplasia and heaping up of the lining epithelium. In a very small percentage of cases the cause of obstruction may be a gall stone in the ampulla or spasm of sphincter. The enzymatic action causes necrosis of the blood vessels and haemorrhage. Adams and Musselman have postulated thrombosis of the pancreatic vein as a cause of pancreatitis rather than a result. Thal maintains that the dermal Schwartzmann reaction and acute haemorrhagic pancreatitis show a similarity in a rapidly developing vascular lesions. Experimental injection with *B. coli* endotoxin in sensitizing and provocative doses has produced identical lesions in the pancreas. In these, necrosis and capillary thrombosis preceded the pancreatitis. Toxins from meningococcus, *E. coli*, *B. proteus* and *Salmonella typhosa* can all produce this reaction, and it is of some significance that they are often-times present in the duodenum.

It is probable that the last word has not yet been pronounced about the pathogenesis of pancreatitis. It is likely that various pathogenic organisms may be the causative factor. Even a virus can probably initiate such processes in the pancreas. Experimentally the use of the Coxsackie virus which is so closely related to the virus of poliomyelitis and the virus of mumps

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is known to produce mild lesions in the human pancreas. Again, certain organic chemicals are known to act selectively upon the cellular components of the pancreas. It is quite common to find pancreatitis in chronic alcoholics. Mallet-Guy and associates produced acute pancreatitis in dogs by electrical stimulation of the left splanchnic nerves. Another interesting hypothesis is to presume a dietary deficiency coupled with the selective action of some toxic substances as a likely cause. Lastly, it may be mentioned that pancreatitis has been known to follow abdominal trauma without external injuries and also to follow operative procedures round about the pancreas.

The pathological changes vary from acute oedema with minute foci of haemorrhage and necrosis confined to a portion of the pancreas to complete destruction of the gland with haemorrhage. Effusion into the peritoneal cavity is common and is serous in character in the milder cases, but more or less haemorrhage occurs into the retro-peritoneal tissues, and may even colour the peritoneal exudate. Patches of fat necrosis appear in the omentum and in the sub-peritoneal region. The resulting fatty acids are fixed by the serum calcium forming calcium soaps. This explains the radio-opaque shadows in cases of mild pancreatic disease which have recovered, and also explains why this radio-opaque shadow is invariably present in a chronic relapsing type of pancreatitis. Depletion of calcium may be so great as to cause a marked fall in serum calcium and predispose to tetany. The purely oedematous forms regress without noticeable permanent damage. The necrotic areas in the gland are replaced by cicatricial fibrous tissues. Stenosis or obliteration of the duct system may result, thus predisposing to further attacks. Large accumulations of extra-pancreatic exudates communicating with the regions of necrosis in the pancreas, in the course of a few weeks or months become encapsulated by granulation and scar tissue. Suppuration may occur in such areas but more commonly these encapsulated pseudo-cysts increase in size displacing the viscera anterior to them until they can be palpated. Patchy destruction of the islets of Langerhans is presumably present.

The clinical aspects vary considerably but commensurate with the varying degrees of severity and the time of observation after the onset of an attack. In the milder form of serous inflammation with oedema there is usually a sudden attack of upper abdominal pain following meals or over-indulgence in alcohol. This is commonly felt in the epigastrium and very often is referred to the back to the left of the spine. Rigidity is minimal and the temperature may be raised 2 or 3 degrees with a variable moderate leucocytosis. There is tenderness on deep pressure over the region between the xiphoid cartilage and umbilicus, more marked to the left of the mid-line. Tenderness to percussion is sometimes elicited in the left costo-phrenic region. There is nausea and some vomiting. Abdominal distention manifests itself quite early but shock is not in evidence except in the most severe forms.

In the acute fulminating attacks the pain is intense and may not be amenable even to repeated administration of narcotics. The severe and extensive exudation causes haemoconcentration and shock and collapse. There is continuous vomiting and finally circulatory collapse ensues.

Between these two extremes, there is a wide spectrum of varying signs and symptoms. Pain however is a constant feature and so also is vomiting. Temperature is raised excepting in the fulminating cases and ranges between 100°-103°F.

The serum amylase is greatly elevated reaching its peak between 24 to 48 hours after the onset, then falling rapidly towards normal. The serum lipase becomes elevated slowly with a peak level in 3 to 4 days and falling more slowly.

Peristalsis diminishes and ileus with progressive abdominal distension appears the day after the onset. If there has been extensive fat necrosis the serum calcium falls by the fourth day of the disease. Thereafter, it may be depressed even to the point of clinical tetany.

With the subsidence of the acute symptoms, an indefinite tender palpable mass may appear in the epigastrium if there has been severe necrosis, in about a week after the onset. This may become smaller, or if infection proceeds apace, increase in size rapidly. A pseudo-cyst increases slowly in size and is less tender. Diabetes mellitus due to diminution or loss of islet function occurs within a few hours after the onset, later either disappearing or becoming permanent.

As pointed out earlier, the first attack may predispose to further ones in a definite proportion of cases. Exact figures are not available, but the frequency in alcoholics is noteworthy. Thus arises the syndrome of chronic relapsing pancreatitis initiated by the first attack and which becomes manifest as each succeeding attack damages the duct system progressively as well as the parenchyma of the gland. Pain in the epigastrium and referred to the left hypochondrium

and back is at first periodic occurring at long intervals. In time the pain becomes more frequent, the attacks less characteristic until distress is almost continuous. Post-prandial and post-alcoholic distress is marked so that an attack can sometimes be brought about almost at will by a good meal or a good 'glass'. Chronic diarrhoea and steatorrhoea occur as the external secretion of the damaged gland gets less. The characteristic elevation of serum amylase seen in the acute attacks diminishes and may even be absent. There is marked weight loss, because of the discomfort caused by eating, and from the diarrhoea and steatorrhoea following even small feeds. In seeking relief from pain many patients are likely to become narcotic addicts. Mild to moderately severe diabetes appears in about a third of these cases as the disease progresses.

The diagnosis of severe acute haemorrhagic pancreatitis gives rise to very little doubt as it is one of the most spectacular of abdominal catastrophes. In the words of Lord Moynihan "The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant on it", all render it the most formidable of such catastrophes. The pain which is of the most severe and agonising kind follows a good meal. As in perforated duodenal ulcer the patient remains motionless. The degree of shock is so profound the like of which is not attained in other disease conditions. A peculiar cyanosis of the face and the presence sometimes of bluish patches of colour on the abdomen are characteristic. The serum and urinary amylase are markedly elevated.

Fortunately, most of the cases do not fall in this category. Mild cases of haemorrhagic and oedematous pancreatitis form an almost infinite gradation into the chronic relapsing forms of the disease.

Acute pancreatitis must be distinguished from other acute upper abdominal conditions, particularly as the patients with acute pancreatitis do not stand surgery well. The chief of these are acute cholecystitis, perforated peptic ulcer, upper intestinal obstruction, mesenteric thrombosis and myocardial infarction, all of which require distinctly different management. In some cases of trauma to the abdomen, acute pancreatitis occurs and may have to be distinguished from intra-abdominal haemorrhage and rupture or perforation of a viscus.

The significance of raised serum amylase and lipase levels cannot be over-emphasized. It forms a fairly specific confirmatory laboratory test. Conditions like renal damage and mumps can also elevate the serum amylase but there are no abdominal symptoms. It must be remembered that the commonest cause for high urine or serum amylase levels is disease of the pancreas. The absorption into the serum may be from the blocked ducts or from the peritoneum flooded by the perforated ducts. The latter will explain how a rise in serum amylase levels is possible in a duodenal perforation, but is not common. Serum lipase levels have also been used as a diagnostic aid. Here the rise is slower and the high level persists for a longer period. Another anomalous condition which may cause confusion is the fact that in acute cholecystitis with stones, temporary blockage at the ampulla of Vater may raise the serum amylase without pancreatitis, and operation should not be withheld in such cases. Administration of morphine or codeine initiates spasm of sphincter of Oddi and may itself contribute to the rise of serum amylase. This will suffice to indicate that serum amylase level should be read with the other symptoms and should not be taken by itself to connote a diagnosis of pancreatitis. In differentiating perforated peptic ulcer from pancreatitis due consideration should be given to the presence of gas under the diaphragm. In traumatic pancreatitis when damage to other organs cannot be ruled out abdominal exploration becomes imperative. We have had one such case in our series, where acute pancreatitis followed injury to the abdomen from the handle-bar of a cycle.

The ileus of chemical peritonitis can produce a picture similar to intestinal obstruction. Amylase determination can give a valuable clue in this condition as well as in mesenteric thrombosis. Coronary occlusion can sometimes be confusing since E.C.G. changes may be induced by the shock associated with pancreatitis and especially when there is a previous history presumptive of coronary insufficiency.

Chronic abdominal pain often related to food for which no other demonstrable cause can be found turns out not infrequently to be of pancreatic origin. Clinical diagnosis in these cases must be made by a process of exclusion or by therapeutic trial. Relief of pain by paravertebral block establishes its visceral but not necessarily pancreatic origin. Anti-secretory and antacid drugs suppress vagal hormonal pancreatic secretion and thus diminish or abolish



## Pancreatitis

the pain of pancreatic origin, but does likewise with pain of gastro-intestinal origin. Radiological appearances are not of positive help, but may enable indirectly to reach a diagnosis by excluding other abdominal conditions. *Nowhere else in the whole realm of abdominal surgery do we find diagnosis so dependant entirely on negative signs rather than on an positive findings.* By a process of careful, meticulous exclusion of other conditions, it is usual to arrive at a diagnosis of pancreatitis. Surgeons will remember the cases in which confident laparotomy for a supposedly different pathology has turned out to be nothing more than chronic relapsing pancreatitis.

**Treatment:** Based on our assumption that the rise in intra-ductal pressure contributes to rupture and escape of enzymes, it is rational in the treatment, to aim at reduction or prevention of enzyme production by the pancreas. Acid in the duodenum is known to stimulate pancreatic secretion; peptones, proteoses and some products of fat digestion also act similarly; the secretion is also controlled by a nervous mechanism via the vagus nerve. To achieve these aims nasogastric suction and the withholding of all food by mouth becomes of prime importance. The stomach should be kept continuously empty to prevent the contents finding their way into the duodenum. The use of anti-cholinergics and antacids helps to neutralise any spill-over, thus suppressing chances of hormonal stimulation.

Supportive measures to combat the lessening of the blood volume must be instituted. The loss of blood protein must also be made good. Blood and blood substitutes thus have a very valuable place in the treatment of pancreatitis. The observations of Kenwell and Wels and of Elliot and his colleagues are all pointers in this direction. We have ourselves found that blood plasma is invaluable in our cases. The loss of chlorides by vomiting, and of calcium by fixation in the shape of calcium soaps, has also to be made good. The patient's total calorie needs have to be maintained by the administration of intravenous glucose or invert sugar. Insulin umbrella becomes a paramount necessity when there is diabetes.

The control of pain is of the highest importance and is imperative in the presence of shock. Morphia by its action on the sphincter of Oddi is not half so effective as large doses of pethidin unless combined with atropine. Para-vertebral splanchnic block gives dramatic relief and is advocated strongly by Dale. Etamon chloride (Parke Davis), a ganglion-blocking agent, has been very effective in our series of cases. The only reaction that is sometimes met with is a fall of blood pressure in some cases. We use this agent in 1 c. cm doses intra-muscularly with the patient in bed for a period of two hours afterwards. The fall of blood pressure is then of no consequence. There is relief of pain for nearly 24 hours and many cases respond well and remain symptom-free after 3 or 4 injections. Rarely have we had occasion to use this more than 7 times in any case. The dose can be safely increased to 2 c.cm as was done in one of our cases without the patient having any distressing symptoms. It can also be continued for 10 to 12 days, if necessary. We are planning to try the effect of 'Buscopan' in our next series of cases.

Antibiotic therapy has no specific role to play unless infection is present, or an abscess likely to result. This may even produce regression without a need for incision. ACTH and cortisone have no place in the therapy of pancreatitis in our opinion. They have been of little use in our observations.

There has been a lot of controversy about the surgical approach to the treatment of pancreatitis. In the milder cases of oedematous pancreatitis which simulate an upper abdominal catastrophe, very often the abdomen is opened and a diagnosis is made. We have done it in our own series. The peritoneum over the pancreas is incised and a drainage tube brought out through the right loin. The relief of tension and the drainage of the effusion minimise the chances of further complications. In our series of cases, though usually there was a continuing discharge of sero-sanguinous material and cell debris for from ten days to two weeks, it then subsides and the wound healed. Only one of our cases had biliary tract disease, which of course, was not treated at the emergency laparotomy. It is our firm conviction that in all cases of pancreatitis, the gall bladder should be preserved at all costs, as it may be required at a later date for short-circuiting procedures.

Removal of stones and drainage of the gall bladder and the common bile duct are enough during the acute phase.

Surgery has its greatest use in the treatment of chronic relapsing pancreatitis. After all, when one considers that the most probable cause of this disease is some form of obstruction associated

with a stimulus to pancreatic secretion, operative procedures aimed at relieving the obstruction may be deemed to be indicated. Medical management with anti-spasmodic and anti-cholinergic drugs and sedatives has not proved useful in these cases, thus providing one more argument in favour of surgery. Thoraco-lumbar sympathectomy from T<sub>6</sub> - T<sub>10</sub> or even up to T<sub>12</sub> has been advocated. Here the aim is to relieve the visceral pain as also the chances of stimuli reaching the pancreas via the splanchnic nerves. Results are stated to be good.

There has been a controversy over the necessity for cholecystectomy when stones are present in the gall bladder. We have followed the views of the Mayo Clinic surgeons in considering drainage sufficient by itself. Mackenzie and Willox however advocate cholecystectomy followed by drainage of the common bile duct. The saving of the gall bladder will also facilitate an operative cholangiogram if necessary, in order to demonstrate stenosis or stones in the duct. A reflux of the dye into the pancreatic duct is usually presumptive evidence of spasm at the sphincter of Oddi, in the absence of mechanical obstruction by stones.

Based on the concept of spasm of the sphincter, Doubilet and Mulholland have performed section of the sphincter of Oddi by either the trans-duodenal or choledochal route. In their hands this operation has been followed by very good results. In a recent paper Mulholland analyses the results and gives the details of the technique. His indications for sphincterotomy are, (1) recurrent pancreatitis, (2) multiple or recurrent common duct stones and ampullary stones, (3) pseudo-cysts of the pancreas and the pancreatic fistulae, and (4) acute cholecystitis. Mulholland is thoroughly convinced that sphincterotomy will arrest the progress of pancreatitis and even allow the pancreas to regenerate. Pseudo-cysts and acute cysts shrink and disappear and are not likely to recur. Special instruments are required for the performance of this operation. Shortening of the gastrohepatic omentum following repeated attacks and adhesions around the duodenum and the pancreas produce anatomical distortion which can make this procedure formidable. The operation is worth attempting and must await assessment at the hands of a larger number of surgeons.

When the obstruction is due to fibrosis and stricture, short-circuiting operations appear to have a rightful place. Cholecysto-jejunostomy or side to side choledochoduodenostomy are attempted. The latter method was adopted by a surgeon known to us in one of his cases. The common bile duct in this case was very dilated and the anastomosis presented few difficulties.

Coffey recommends transduodenal exploration of the pancreatic duct to establish the cause of obstruction. He uses a polyethylene catheter of small diameter to explore and irrigate the duct. The use of an opaque medium introduced through this can reveal the presence of stones or obstruction.

Duval, Zollinger, Aird and Buckwalter and others have been advocating the retrograde drainage of the obstructed pancreatic duct by a pancreatico-jejunostomy. The tail of the pancreas is sectioned and the cut end is inserted end to side in the jejunum or end to end by means of a Roux-Y. During the operation the distal end of the duct can be probed to remove any residual calculi.

Cannon thinks that ligation of the pancreatic duct with destruction of the acinar portion and cessation of exocrine function will cure pancreatitis. The endocrine function however is preserved. Ligation of the duct is not an easy procedure especially when anatomical distortion is present and in any case the ligature of the duct of Wirsung by itself may not be effective in all cases. This however remains an interesting innovation.

Pseudo-cysts and cysts are dealt with by prolonged drainage, marsupialization or internal drainage by anastomosis to the jejunum or stomach as the case may be. The results have been uniformly good.

Partial or total pancreatectomy, when there is gross destruction of the gland or calcification, and when the pain is constant in spite of treatment, has been advocated. To us a total pancreatectomy seems to be an unduly drastic measure. A partial pancreatectomy is probably justifiable, and even then only when other measures have failed to give relief.

Summing up the greatest field for surgery is in chronic relapsing pancreatitis while the acute oedematous type and the haemorrhagic types demand medical measures and expectant treatment.

We feel that the treatment of pancreatitis is still unsatisfactory and though a multiplicity of measures are advocated and available, the selection depends greatly on the individual surgeon.

## Pediculosis, Crotonyl N-Ethyl Toluidine in

An awareness of the frequent occurrence of this condition and its various manifestations will result in earlier diagnosis and proper treatment. In its wake this will bring to fruition the two-fold objective of minimising the slide to the chronic relapsing state, and greater experience in the surgery of the pancreas.

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## PEDICULOSIS, CROTONYL N-ETHYL TOLUIDINE IN

K. C. Sahu

Following reports of the high acaricidal effect of Crotonyl-N-ethyl toluidine in human beings, the drug under the proprietary name Eurax was given a clinical trial in nine cases of pediculosis at the Skin Clinic of S. C. B. Medical College and Hospital, Cuttack. It was found to be a good parasiticide for pediculosis corporis and capitis. Ten per cent of this ointment incorporated into a non-greasy, non-irritating base is effective against pediculosis and has got a bacteriostatic effect on strepto- and staphylococci, producing impetigo of the scalp due to scratching. It does not irritate or harm the scalp and the skin. It is well-tolerated by both children and adults and no irritation or exanthematic reaction of the skin were experienced. No toxic manifestations of resorption were observed. It has got antipruritic effect. It does not soil the clothes. It is simple and odourless, and does not irritate the skin even on prolonged application. In about 3-4 days of application of this drug, the patients got rid off pediculosis.

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## PELVIC TUBERCULOSIS IN GYNAECOLOGY—See TUBERCULOSIS, PELVIC, IN GYNAECOLOGY

## PEPTIC ULCER, MEDICAL MANAGEMENT OF

N. J. Modi

In an analysis of 3011 cases of peptic ulcer, Ian Aird et al<sup>1</sup> have shown an increased incidence of blood group O, and it appears that persons with blood group O are about 35 per cent more likely to develop peptic ulcer than others.

Clark et al<sup>2</sup> in their study of 1615 ulcer patients confirm the findings of Ian Aird and others. They found higher incidence of group O amongst patients with duodenal ulcer as compared with controls, gastric ulcer cases did not show such higher incidence, and suggest that gastric and duodenal ulcers are probably inherited independently.

*Hypersecretion of Acid*: Hunt, et al,<sup>10</sup> investigating the nature of hypersecretion of acid in patients with duodenal ulcer observe that it could be due to increased activity of the gastric mucosa or to an abnormally large number of parietal cells. Their study based on maximal stimulation with histamine covered by antihistamine, suggests that the high basal secretion of acid in them is due to their having a greater number of parietal cells and that excessive activity of the psychic, gastric or intestinal phases of secretion were not the factors for hypersecretion.

*The mechanism of pain in peptic ulcer* is still not clear. There are three theories trying to explain the mechanism: 1. Acid theory—The acid of the gastric juice irritates the ulcer base and causes pain. 2. Motility—Pain is due to normal or abnormal muscular activity of the stomach and

duodenum. 3. Inflammatory reaction around the ulcer is the cause of pain. The relation of pain to acidity or motility is denied by Smith<sup>17</sup> from his study of 27 patients. In spite of absence of free acid in the patients pain was present ; he also found that the relation of pain to motility was poor. He emphasizes the local inflammatory reaction—the degree of oedema and engorgement of the ulcer area, and its variations, also the sensitivity of the ulcer—as the explanations for the pain in peptic ulceration.

Farmer<sup>7</sup> described the pain in peptic ulcer to be gnawing, burning, cramp-like, boring or cutting and present only when free hydrochloric acid is present in gastric contents; it can be eliminated by its neutralisation or its removal from the stomach by emptying. Hyperperistalsis or muscle spasm by themselves are not responsible for pain but in the presence of free acid they may increase the pain. The pain of gastric and duodenal ulcer has characteristic localisation and radiation; it usually occurs in bouts with periods of freedom varying from a month to several years.

Doll et al<sup>4</sup> carefully studied the comparative effect of the bland standard ulcer diet and normal diet except fried foods in 164 gastric ulcer patients and 50 of duodenal ulcer, and the results showed slightly more number of patients in the completely healed group on the almost normal diet ; also the gain in weight was better in this group, but on the standard ulcer diet more patients were free from pain throughout treatment. This study at the end of one year also showed that dieting with bland foods did not increase the speed of healing of peptic ulcer.

Doll et al<sup>5</sup> gave continuous intragastric milk drip to 164 patients of gastric ulcers ; to 40 patients 6 pints milk a day was given and to another 40 in addition to 6 pints of milk 40 g of sodium bicarbonate was added to the drip. Ulcers were healed in a month in equal number of patients, but pain was relieved more rapidly with milk drip than without it and the alkaline milk drip was even better for those in whom pain persisted even after rest in bed.

Snapper et al<sup>16</sup> have reported the following adverse effects in patients who were treated with large amount of milk, calcium and alkalis for peptic ulcer: 1. A widespread calcinosis in the subcutaneous tissues and in the kidneys. 2. The serum calcium and phosphorus may be elevated, mild alkalosis and anaemia may be found. 3. Even uraemia may supervene in severe cases. By stopping milk and alkalis in the early stages it can be prevented.

Scholz et al<sup>15</sup> reported more cases of 'milk-alkali syndrome' due to taking excessive milk and alkali for treatment, this leads to calcium retention and organic changes in the kidneys. Anorexia, memory defects, marked polyuria or increase in blood urea point to this condition. It is often mistaken for chronic nephritis, but on investigating a high serum calcium is found. The patient improves on decreasing milk and dropping the alkalis.

Price et al<sup>13</sup> studied 30 cases—15 each of gastric and duodenal ulcer, by giving a continuous milk and alkali drip throughout 24 hours and found that nearly 60 g a day of alkali was required for effective continuous neutralisation of gastric contents in gastric ulcer and great deal more in duodenal ulcer.

David et al<sup>3</sup> have tried some cholinergic drugs for suppression of gastric acidity to pH 4.5 or higher. The optimum effective dose (O.E.D.) was always one which caused dryness of the mouth. He tried tricyclamol methyl sulphate (150 mg to 500 mg), piperphenidol bromide (50 to 400 mg) and propantheline bromide (30 to 120 mg). The effective dose varied with each patient.

Sandweiss et al<sup>14</sup>, in discussing recent advances in the medical treatment of peptic ulcer, summarise their views as follows :

1. A diet of soft foods with frequent small feedings, calculated to supply the complete nutritional needs of the patient ; the inclusion of foods that absorb or chemically combine with hydrochloric acid and the exclusion of foods that act as mechanical, chemical and thermal irritants. The possible risk of coronary atherosclerosis due to high fat diet should be kept in mind.

2. Frequently giving sufficient liquid non-absorbable antacid (15 c.cm of aluminum hydroxide gel combined with milk of magnesia) which produces a minimum, if any, acid rebound and is also free from the danger of producing systemic alkalosis or renal changes.

3. Oral anticholinergic drugs with potent antisecretory and motor depressant properties, associated with a minimum of undesirable side effects. Hormonal agents like enterogastrone and urogastrone for human use are still not available though they have proved effective

## Peptic Ulcer, Medical Management of

antiseecretory agents in dogs when given intravenously. Enzyme inhibitors like acetazolamide (Diamox) and p-chloromercuribenzoate as antiseecretory drugs promise a new field.

4. Abstinence from the use of tobacco, alcohol and caffeine-containing beverages.

5. Insist on using sedatives—phenobarbital ( $\frac{1}{4}$  to  $\frac{1}{2}$  gr) three times daily and nembutal ( $1\frac{1}{2}$  gr) at bed time and also physical rest must be taken.

6. Attend to emotional conflicts, which exist in good many patients. Prevention of recurrences—the dictum “once an ulcer, always an ulcer” is well-known. The following programme is advised :

- An adequately nutritious diet, with specific restrictions for a period of at least six months to one year. Exclude highly seasoned and spicy food indefinitely.
- Abstinence from the use of tobacco, alcohol and caffeine-containing beverages.
- Resume rigid ulcer regimen if symptoms of ulcer recur or during periods of stress and strain.
- Increase physical and mental rest, avoid fatigue and overwork.
- Prompt treatment of acute infections.
- Careful use of steroid hormones, butazolidin, hydralazine and hexamethonium salts.

Modi<sup>12</sup> stressed the role of continuous hourly gastric analysis by investigating some peptic ulcer patients for a period of 2 to 7 days round the clock. The best results were obtained by Sippy's diet combined with drugs. The clinical features of 25 cases of peptic ulcer were also presented.

The current status of the newer anticholinergic drugs in peptic ulcer is reviewed by Kirsner et al<sup>11</sup>. These drugs interfere with the transmission of nerve impulses mediated by acetyl choline at the neuro-effector junctions of postganglionic cholinergic nerves. By inhibiting the vagal mechanism they decrease the output of hydrochloric acid and thereby facilitate healing of the ulcer, similarly by blocking vagal stimulation of smooth muscle, gastro-intestinal motility is diminished, also a therapeutically useful effect produced. These drugs should be used as adjuncts to other recognised methods of treatment, they are prescribed orally, before meals, as they are more effective against basal secretion rather than against food-stimulated secretion ; a large dose, double or more, is given at night to counteract nocturnal hypersecretion. The effective dose is one which gives minimal side effect. They must be taken continuously for long periods, and there is no proof of drug tolerance. The outstanding effect is the prompt relief of pain. Clinical evaluation of anticholinergic drugs in peptic ulcer is hazardous and difficult. By using “double blind” technique for a period of two to three years in selected mild uncomplicated ulcer cases, more precise results may be obtained.

*Side effects*, many and undesirable, are as follows :

Dryness of mouth, bad taste, blurring of vision, constipation, delay in urination, dryness of skin, headache, dizziness, weakness, drowsiness, tremor, nausea, vomiting, heartburn, palpitation and flushing of face, rarely conjunctivitis, polyuria, loss of libido and mental confusion. The output of saliva is regarded as a good clinical index of systemic parasympathetic inhibition.

The following drugs are some of those used in the treatment.

Drug	Oral gastric antiseecretory potency	Side effects	Effective or maximum single dose in mg	Recommended oral daily dose in mg
<b>A. Potent inhibitors</b>				
1. Pamine (Upjohn) .. ..	Good	Moderate	10	10 - 30
2. Skoplate (Strassenburgh) ..	Good	Moderate	8	6 - 12
3. Maltocran (Maltbie) .. ..	Good	Moderate	50	120
4. Marplan (Hoffman la Roche)	Good	Moderate	5	15 - 20
5. Probanthine (Sevell) .. ..	Good	Severe	30	75 - 240
6. Tral (Abbot) .. ..	Good	Moderate	50	100
<b>B. Moderate antiseecretory activity</b>				
1. Antrenyl (Ciba) .. ..	Moderate	Severe	25	40
2. Monodral (Winthrop) .. ..	Moderate	Moderate	10	15 - 20
3. Pathilon (Lederle) .. ..	Moderate	Moderate	100	100 - 200
4. Piptal (Lakeside) .. ..	Moderate	Moderate	25	25
5. Cotranul (Squibb) .. ..	Moderate	Severe	100	400
6. Tricoloid (Burroughs-Wellcome)	Moderate	Moderate	150	300

Banthine, Prantal, Darstine and Elorine are relatively ineffective.

The authors summarise their experience by observing that these drugs are better than tincture belladonna, atropine and banthine; by injection they produce achlorhydria for hours, and by mouth they are good adjuncts, lower the acidity and give more efficient neutralization of gastric contents.

Roter tablets which contain magnesium carbonate pond. (400 mg), sodium bicarbonate (200 mg), calamus (25 mg), frangula (25 mg) and bismuth subnitrate (350 mg) were used in 98 cases of peptic ulcer with a satisfactory response in 90 per cent of patients, with a relapse rate of 57 per cent in the first year<sup>9</sup>.

Medical management of massive haemorrhage from peptic ulcer (Gray et al<sup>8</sup>)—It is the commonest cause of bleeding from the upper gastro-intestinal tract. It is believed that if the bleeding is terminated by medical means, it gives the lowest possible mortality. The following is the basis of medical management.

1. Replacement of blood loss and treatment of shock—promptly start 5 per cent glucose in normal saline infusion and then give slowly repeated blood transfusions—this combats shock and exsanguination. Continue blood transfusions as long as (a) shock persists, (b) systolic blood pressure is below 90 to 100 mm Hg, (c) pulse rate is greater than 120 per minute or is rising or (d) the hematocrit reading is 30 or below. Avoid overburdening the heart and circulation, particularly in the aged or cardiac patients. Ventricular fibrillation or asystole may be caused by giving transfusion too rapidly.

2. Acid neutralization, as complete and constant as possible is done by small hourly feedings of equal parts of warm milk and cream—1 to 4 oz, from 7 A.M. to 10 P.M. and 2 hourly feedings of 6 to 8 oz at night.

Colloidal aluminium hydroxide as an antacid is given with the feeds around the clock to neutralise high nocturnal gastric secretion. If there is persistent nausea and vomiting nothing should be given by mouth, and the patient maintained on parenteral fluids, sedation and antispasmodics, and later on small feedings of warm skimmed milk are begun. Gastric aspiration may be needed if pyloric obstruction is present. This diet supplies about 2400 calories with 60 g of protein daily. Oral feedings are preferable to the intragastric drip. Calcium carbonate 2 to 4 g or Sippy powders 2 g are advocated for marked hyperacidity if the problems of alkalosis or sodium administration are not there. Magnesium oxide 2 g or milk of magnesia,  $\frac{1}{2}$  to 1 oz may be needed for constipation.

Douthwaite and Booth<sup>6</sup>, in search for inhibitors of gastric secretion at the cellular level, gave mersalyl, a mercurial diuretic, by gastric route to patients with duodenal ulcer and found absence of hydrochloric acid secretion for two hours. This finding has no practical importance.

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### PERICARDITIS

L. K. Ganguli

**Aetiology:** The aetiology of pericarditis has been the subject of a recent symposium<sup>1</sup>. Based on pathological studies only, it appeared that tuberculosis was the first in the list followed by rheumatic infection. A clinical study of a separate series of cases showed that out of 40 cases of pericarditis of various aetiology 25 cases were of tuberculous origin. Deterling and Humphreys<sup>2</sup> have analysed 416 cases with definite evidence of pericarditis. The period covered was from 1930 to 1954. According to them 139 cases were of rheumatic origin, 53 of tuberculous origin (42 cases proved), and amongst others 57 cases were due to uraemia and 48 were idiopathic.

**Chronic Constrictive Pericarditis:** The aetiology is obscure in the majority of cases. Amongst 416 cases<sup>2</sup> 30 patients (25 confirmed) had constrictive pericarditis. Out of 25 proved cases 11 had radiologically calcification of the pericardium. Tuberculosis as the aetiological factor could be proved only in 4 cases. According to them ready acceptance of tuberculosis as a proved cause of chronic constrictive pericarditis is very difficult to correlate and prove in all cases, on the existing presumptive evidence, though tuberculosis is the most common cause. The authors conclude that there are certain important factors in the development of the clinical syndrome of constrictive pericarditis. They are: (1) Prolonged exposure of the pericardium to irritants (tuberculosis, foreign bodies, organising blood clot); (2) Extensive pericardial involvement and (3) Associated myocardial damage as well as pericardial compression.

Development of constrictive pericarditis may not take a long time from the initial onset of the disease. Chatterjee et al<sup>3</sup> have reported a case who developed pericardial effusion and then imperceptibly passed into constrictive pericarditis within a few months. The patient had immense clinical improvement after surgery.

Gunnar et al<sup>4</sup> have reported a rare and interesting case of pericarditis due to primary amyloidosis. The aetiology was confirmed at autopsy. The patient had all the similarities in the clinical and the cardiodynamic findings to those of constrictive pericarditis.

**Idiopathic Pericarditis:** In recent years reports on idiopathic pericarditis are appearing in fair numbers. The aetiology of these cases of idiopathic or benign pericarditis is always of interest. Dressler<sup>5</sup> has drawn attention to certain facts which are well worth consideration. In a study of 12 cases of idiopathic pericarditis he encountered the main symptom of severe and occasionally excruciating pain or of pressure, in all his cases. A tendency to recurrence was also a prominent feature, with a 50 per cent relapse rate in 12 patients having a total of 42 attacks. The points of resemblance, in clinical and laboratory findings, between idiopathic pericarditis and postcommissurotomy syndrome, have been brought out by the author. Moreover, the lack of therapeutic effect with drugs like sulphanilamides, penicillin and streptomycin and a dramatic effect with cortisone is a feature also observed in postcommissurotomy syndrome. The author believes in an identical aetiology in both the cases.

**Diagnosis:** Calcification of the pericardium has been a valuable radiological finding in the diagnosis of pericarditis of pathological origin. The fact that calcification of pericardium may occur in apparently healthy people causes more difficulty in arriving at a conclusion. Mathewson<sup>6</sup> has presented 5 such case reports of apparently healthy individuals who had pericardial calcification, as demonstrated by certain abnormal E.C.G. changes, X-ray appearance (4 cases) and by autopsy findings (one case).

There were no changes in the cardiac rhythm, P waves, QRS complex and in the voltage. Depression of RS-T segment in L2 and the left precordial leads was detected in 3 cases. Flat or inverted T in the limb leads and a variable number of precordial leads occurred in 4. One patient had a normal E.C.G.

**Treatment:** Treatment of tuberculous pericarditis with combined antibiotic and chemotherapeutics is satisfactory. Goyette et al<sup>7</sup> reports of 27 cases of primary tuberculosis of the pericardium out of which tubercle bacilli were demonstrated by culture in 13 patients. The therapy consisted of intermittent use of streptomycin, 2 g, on every third day with 12 g PAS and in some cases 300 mg isoniazid a day. The regime was continued for 6 months even after all the signs of activity had ceased. Twenty-one patients fared well. Constrictive pericarditis developed in 5 and one died due to overwhelming infection. Surgery combined with chemotherapy is recommended by the authors in progressive congestive failure in spite of an active lesion. Ghosh<sup>8</sup> has reported six cases of tuberculous pericarditis (4 with effusion,

2 adhesive) treated with streptomycin and isoniazid. Out of the 6 cases reported by him in one case autopsy revealed tuberculous granulation tissue in the heart, lungs, liver, spleen and lymph glands; one case had tuberculosis of the peritoneum and the cervix of the uterus and two cases showed involvement of other viscera. Combined therapy caused rapid improvement in four cases.

In spite of proper and adequate use of antibiotics and chemotherapeutics in the treatment of purulent pericarditis, pericardiostomy is sometimes necessary. Moreover, adhesive pericarditis as a sequela poses a problem. Basu Roy<sup>9</sup> has advocated the use of streptodornase and streptokinase to liquefy purulent exudate in addition to the use of antibiotics. In a case reported by him he introduced 100,000 units of streptokinase and 25,000 units of streptodornase in 10 ml of normal saline, in the pericardial cavity, 24 hours previous to aspiration. The end results were good.

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**PHARYNX, SUBMUCOUS FIBROSIS OF**—See SUBMUCOUS FIBROSIS OF MOUTH AND PHARYNX

**PHENYLKETONURIA**—See ALKAPTONURIA AND PHENYLKETONURIA

**PHOSPHOROUS COMPOUNDS, ORGANIC, TOXICOLOGY OF**—See TOXICOLOGY OF NEW ORGANIC PHOSPHOROUS COMPOUNDS, etc.

**PHYSIOLOGY OF THE ALIMENTARY SYSTEM**—See ALIMENTARY PHYSIOLOGY

**PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM**—See CARDIOVASCULAR PHYSIOLOGY

**PHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM**—See NEUROPHYSIOLOGY

**PHYSIOLOGY OF THE HIGHER FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM**—See CENTRAL NERVOUS SYSTEM, HIGHER FUNCTIONS, PHYSIOLOGY OF

#### PITUITARY GLAND

B. B. Mukherji

**Hypophysectomy for Cancer.**—The subject has been discussed in details in a leading article in *Lancet*, March 9, 1957. Hypophysectomy has so far been found beneficial only in treatment of patients with carcinoma of the breast. It is much less promising in carcinoma of the prostate while it has been found to be of no benefit in hypernephroma, carcinoma of the thyroid, malignant melanoma and adrenocortical carcinoma with Cushing's syndrome.

Luft et al<sup>1</sup> recorded objective remissions after hypophysectomy in 22 out of 41 cases (54 per cent) of breast carcinoma. Some of the remaining patients had temporary symptomatic improvement. The average duration of remission was 17 months. Pearson et al<sup>2</sup> noted subjective remission after hypophysectomy in 21 out of 41 cases (51 per cent) of breast carcinoma and the period of remission averaged 6.5 months. Kennedy<sup>3</sup> similarly recorded remission in 18 out of 28 cases (64 per cent) lasting for an average period of 7.6 months. Atkins et al<sup>4</sup> have compared the results of hypophysectomy and adrenalectomy in combination with oophorectomy in breast carcinoma taking 30 cases in each group. The overall results of hy-



## Pituitary Gland

hypophysectomy seemed superior to those of adrenalectomy with oophorectomy and the patients survived on the average of 4 months longer after hypophysectomy than after adrenalectomy with oophorectomy. The authors however remarked that the differences were not statistically significant.

Attempts have been made to find out satisfactory means of predicting which patients with breast cancer will respond to hypophysectomy or to adrenalectomy. Measures which are likely to be of value in this respect are: (1) Allen and his colleagues<sup>5</sup> have noted that the ratio of 11-desoxy-17-ketosteroids to 11-oxygenated or 11-hydroxylated 17-ketosteroids was greater than 1 in 11 patients who benefited from hypophysectomy or adrenalectomy and less than 1 in 4 patients who did not respond. (2) It appears from the series of observations made by Scowen and Hadfield,<sup>6</sup> Hadfield and Young<sup>7</sup> and Hadfield<sup>8</sup> that patients with a high output of mammatrophin (which is probably prolactin) usually have a significant regression of the growth after hypophysectomy. (3) Emerson and Jessiman<sup>9</sup> suggest that if a provocative dose of oestrogen increases the urinary calcium excretion or cortisone reduces the excretion, it is likely that the tumour is hormone-dependent and will respond to adrenalectomy. This study of calcium balance will be of value when there is osteolytic metastasis. (4) Luft et al<sup>1</sup> have made the tentative suggestion that in post-menopausal women, the prospects of benefit after hypophysectomy become progressively less and that women after 60 are very unlikely to respond. They also suggest that response is much less satisfactory when the growth has been present for a long time. (5) Kennedy<sup>3</sup> is of opinion that pre-menopausal patients who respond to therapeutic castration will probably respond to subsequent hypophysectomy and that post-menopausal women responding to oestrogens or androgens will also probably improve after hypophysectomy. (6) Pearson et al<sup>2, 10</sup> state that a patient responding favourably to androgen therapy or oophorectomy is likely to respond to hypophysectomy but failure to respond to androgens or oestrogens does not exclude the possibility of subsequent response after hypophysectomy.

In attempts to find out which patients with breast cancer will respond favourably to hypophysectomy, certain other facts have come to light. Thus Greenwood and Balbrook<sup>11</sup> have shown that excretion of oestrogens continue even after hypophysectomy. (The same authors<sup>12</sup> have also found that oestrogen excretion may continue after adrenalectomy and oophorectomy). The authors are of the opinion that failure to respond favourably after these operations does not necessarily mean the oestrogen independence of the tumour. It is then possible that there is some accessory anterior pituitary tissue in certain persons which is active throughout life or becomes active after hypophysectomy. Boyd<sup>13</sup> has examined the roof of the nasopharynx from which the anterior pituitary develops embryologically and has found groups of highly differential anterior pituitary cells.

Russel<sup>14</sup> has suggested that low-stalk section which is a much easier operation than total removal of the gland can serve the purpose of hypophysectomy. In two of his 3 cases, low-stalk section led to complete necrosis of the anterior pituitary. A mid-stalk section results in reduction of volume of anterior pituitary by 68 to 83 per cent as shown by Campbell and Harris<sup>15</sup>. It is possible that enough pituitary tissue may then be left behind to nullify the beneficial effects of the operation.

In the early days of hypophysectomy, some of the disappointments might have been due to incomplete removal of the anterior pituitary. Completeness of hypophysectomy will be noted from appearance of signs of hypopituitarism. Adrenal insufficiency appears in the course of 2 to 3 days if no cortisone is given. Pearson et al<sup>2</sup> and Luft et al<sup>1</sup> suggest 200 to 300 mg of cortisone daily starting on the day before operation and gradually bringing it down to 50 mg daily by the end of the first week. Hypothyroidism always develops and is usually detected clinically after 1 to 2 months and sometimes a few months later. 60 to 180 mg of thyroid are needed daily to maintain an euthyroid state. Baron<sup>16</sup> and Kennedy<sup>3</sup> note that a mild degree of diabetes insipidus develops in 50 to 60 per cent of cases. Polyuria can often be controlled by posterior pituitary snuff or by injection of pitressin tannate in oil. Defects in the visual fields, anosmia, oculomotor palsy, etc. are the sequelae that are met with from time to time.

**Coma in Hypopituitarism.**—Sheehan<sup>17</sup> has given an account of coma in hypopituitarism in which he stresses on the following diagnostic points : (1) absence of pubic hair; (2) small-

ness of the thyroid which is not palpable; (3) atrophy of the genital organs. The vulva and the vagina are atrophic and the cervix and the uterus small; (4) clinical history: post-partum type being most common, there is usually a history of severe obstetric haemorrhage or shock followed by permanent ill health and amenorrhoea and (5) if facilities are available for pathological investigations, estimation of blood sugar and other examinations should be carried out. Owing to misleading accounts of hypopituitarism which were current in text-books the author has made a particular reference to the following points: (a) the patient's nutrition is usually satisfactory; (b) these patients do not show premature senility; (c) the state of the teeth is quite irrelevant.

Sheehan describes the following broad clinical types of coma in hypopituitarism: (1) Pyrexial, the temperature usually varying between 102° and 105° F. The coma is usually of gradual onset and tends to be of spastic type. (2) Hypothermic, the temperature usually recorded is 96° to 97° F. The onset is usually gradual and the coma tends to be flaccid in nature. (3) Hypoglycaemic—blood sugar is usually 15 to 30 mg per cent and in less typical cases as high as 50 mg per cent. The coma tends to develop suddenly sometimes early in morning and may be associated with severe sweating. (4) Other types—The coma is usually preceded by a few days of vomiting. Temperature is normal and blood pressure rather subnormal.

*Hypopituitarism:* Van Arsdel, Jr. and Williams<sup>18</sup> evaluated various tests in differential diagnosis in 62 patients with Simmonds' disease and 33 with primary hypothyroidism. The authors found that the follicle-stimulating hormone (FSH) assay for differentiation of primary myxoedema and Simmond's disease is of little value in the male and pre-menopausal female because of relative insensitivity of the assay method and the tendency for pituitary secretion of gonadotropins to be depressed to an undetectable level in primary myxoedema. The urinary gonadotropic level in post-menopausal female is normally considerably raised. Even in primary myxoedema it is significantly high. Hence failure to demonstrate gonadotropin in the urine in these cases is an almost certain indication of hypopituitarism.

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#### PITUITARY TREATMENT OF LEUCODERMA—See LEUCODERMA, PITUITARY TREATMENT OF

#### PLACENTA PRAEVIA

K. Bhasker Rao

This is present in about 12-15 per cent of antepartum haemorrhages. Digital examination is the surest but the most dangerous way of diagnosing this condition. Hence different methods of localisation of the placenta have been devised varying from contrast radiography, soft tissue X-ray techniques, to injections of radioactive Na<sup>24</sup>. From the different densities of soft tissues—uterus, placenta, amniotic fluid—the placenta can be visualised. It occupies space. If it is in the lower uterine segment depending on whether it is anteriorly or posteriorly placed, it displaces the presenting part from the pelvic brim. By studying the relationship of the presenting part to the pelvic brim in the erect and tilted lateral radiographs, and also by the presence of any calcified shadows, the placenta can be located. An almost cent per cent accuracy has been claimed<sup>1</sup>. Still, as Macafee<sup>2</sup> points out, there are fallacies as in placenta membranacea or in cases of loaded bowel or distended bladder.

In those cases where pregnancy is over 36 weeks it has to be terminated once the diagnosis is confirmed. But in those cases where pregnancy is 30-34 weeks, conservative line of

## Plastic and Reconstructive Surgery

treatment is followed. In the absence of bleeding, she is kept under observation and her general condition is improved. With the expectant line of treatment, the foetus is given a chance to grow upto 37 weeks. It is essential that no vaginal examination is done by a midwife, general practitioner or house-staff till the bleeding warrants termination of pregnancy and even then it is done only in the operation theatre after blood transfusion has started. In minor types of placenta praevia, ARM alone is sufficient to control bleeding; and if it does not, caesarean section is done. Willett's forceps is fast falling into disrepute. In all major types of placenta praevia, lower segment caesarean is performed. Macafee reported 1553 cases of placenta praevia with 0.9 per cent maternal deaths and 22.9 per cent foetal mortality. Latest results<sup>3</sup> from his own hospital are better—200 cases, with caesarean section rate of 76 per cent, gross foetal mortality of 11.9 per cent, but no maternal death. These splendid results have been obtained by expectant line of therapy, extended use of caesareans and improved blood transfusion facilities.

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## PLASTIC AND RECONSTRUCTIVE SURGERY

R. J. Maneksha

### Bed Sores

Sores in paraplegics are due to intrinsic and extrinsic factors. Lowering of tissue resistance to pressure occurs during spinal shock due to loss of vasomotor control, at the same time there is loss of sensation of the paralysed part. Important extrinsic factors are maceration of skin and pressure.

In the early stages of paraplegia sores are more common on pressure points like the sacrum, the trochanter, the ischium, etc., while later on due to spasticity the inner sides of knee and ankle are involved. The pathological changes in the tissues are mentioned by Guttman. The general treatment consists of improving the state of nutritional deficiency, maintenance of nitrogen balance and treatment of anaemia.

For local therapy prevention is better than cure. Frequent changing of the patient's position during day and night is essential.

After the sore has developed early excision of slough and drainage of abscesses is indicated.

For marked spasticity intrathecal alcohol injection is better than anterior or posterior rhizotomy.

Plastic procedures like rotation skin flaps are performed only after the general condition of the patient has improved.

### REFERENCE

- Guttman, L.: The problem of the treatment of pressure sores in spinal paraplegics, *Br. Jour. of Plastic Surgery*, 196-198, 1956.

## The Treatment of Pressure Sores in Paraplegic Patients

The preventive treatment must begin on the first day of the injury to the spinal cord. All patients are ideally treated in a spinal injury unit.

Local initial treatment of the sore includes cleaning the margins with one per cent cetrimide and dried with methylated ether. The ulcer is cleaned with hydrogen peroxide and saline and dressed with eusol. Local antibiotics are substituted 48 hours before the operation. Spontaneous healing often occurs, if not, free grafting is done. For sacral sore, definitive treatment in the form of double rotation flaps, is advised. Haemostasis under the flap is important. Lateral drainage is maintained for 4 days.

In trochanteric sores infection may spread to the neck of the femur and the hip joint. The trochanteric sore is closed with a transposition flap with its base directed upwards.

The ischial sore is a late development when the patient is up and about on a wheel chair, hence the patient should be made sore-conscious during his rehabilitation period and also for the remainder of his life. In the beginning, the bursa is affected whilst later on the bone is affected.

The skin edges of the ulcer are undermined for a fairly long distance. For treatment the patient is put to bed, never permitting any weight-bearing at the affected tuberosity. Excision of the affected skin, bursa and bone with closure of the skin by direct suture or by flaps from the postero-internal aspects is advocated. The author concludes that all ulcers can be closed with the possible exception of the trochanteric, leading into an infected hip joint.

**REFERENCE**

Osborne Rowland : *Br. Jour. of Plastic Surgery*,  
p. 214, 8, 1956.

**Reconstruction of the Oral Cavity in the Treatment of Cancer**

Milton and Desprez of the John Hopkins Hospital advocate wide excision of the malignancy which must be combined with primary reconstruction as late repairs are more difficult due to contraction of tissues and loss of the patient's morale.

The authors' series include 154 cases and the majority were after failure of irradiation (69 per cent); a three year survival without evidence of recurrence was obtained in 43 per cent of the operated cases.

Reconstructive procedures for the loss of mucosa, tongue, mandible as well as facial nerve are well discussed in the minutest detail.

**REFERENCE**

Edgerton, Milton T. and Desprez, John D.: *Plastic and Reconstructive Surgery*, p. 89, 19, 2, 1957.

**Cleft Palate and Lip**

*Diagnosis, Prognosis and Treatment of "Palato-Pharyngeal Incompetence" with Special Reference to Radiographic Investigations:* Colman defines palato-pharyngeal incompetence as the condition in which the soft palate fails to meet the posterior pharyngeal wall. The cause may be extrinsic or intrinsic.

Radiography helps in the assessment of the incompetence of the sphincter. A barium suspension with picric mucilage is injected in each nostril after which the patient is made to have an "explosive cough", thus coating the barium over the roof and the posterior wall of the nasopharynx. Similarly Micropaque (Damancy) or Fotogel (Evans) may be used.

Very interesting line diagrams of the X-ray plates are given showing the length and mobility of the soft palate, at rest and during phonation of different words, before and after veloplasty and pharyngoplasty.

Lateral radiographs have been found useful by Colman to check the result of operations, to indicate the need for speech therapy and to confirm the results of speech therapy.

The author advises a complete radiographic analysis in addition to routine clinical examination in all palatal defect cases.

**REFERENCE**

Colman, James: *Br. Jour. of Plastic Surgery*,  
p. 265, 8, 1956.

**Haemangiomas**

*The Treatment of Haemangiomas:* J. R. Lewis divides haemangiomas into capillary and cavernous. Unless the lesion is easily excised, the bulky haemangiomas are best treated by injection of a sclerosing solution. Injections are given at intervals of two weeks.

The author uses 5 per cent sodium morrhuate with equal amount of 2 per cent procaine and 150 units of hyalase, 50 c.cm. of the solution. The hyalase increases the diffusion of the solution and minimizes any necrosis of tissues. Pressure dressing is maintained for 24 to 48 hours.

The flat type of haemangioma of the "port wine" type should be excised if it can be done without leaving deforming scars. Some of these types of tumours have improved by surgical abrasion under ethyl chloride spray.

**REFERENCE**

Lewis, John R. Jr.: *Plastic and Reconst. Surgery*.  
p. 201, Vol. 19-3-1957.

## Plastic and Reconstructive Surgery

### Mandible

*The Surgical Treatment of Chronic Derangements of the Temporomandibular Joint* : Subluxation or "clicking jaw" is the most frequently seen pathological condition involving the temporomandibular joint. The authors observed 27 cases of which 70 per cent were in young women. Pain was present in 50 per cent, while clicking in 22 per cent. The common aetiology is either dental or from external trauma. The case is first seen by the dentist and treated for dental aetiology. Only seven of the 27 cases required operation after conservative treatment e.g., local rest and avoidance of hard food had failed.

The joint is approached through a preauricular approach. The facial nerve branches are carefully preserved. The temporomandibular ligament is reflected from the zygomatic arch, capsular ligament is divided and the whole disc is excised. The temporomandibular ligament is stitched more posteriorly and the joint kept at rest for three weeks with interdental splintage.

#### REFERENCE

Bruce, Trabue John, Leech Thomas, *Plas. & Reconst. Surgery* p. 131-19-2, 1957.

*An Experimental and Clinical Evaluation of Autogenous Dermal Grafts used in the Treatment of Temporomandibular Joint Ankylosis* : The problem of restoring ankylosis of the temporomandibular joint has been a challenge to surgeons during the last century. Insufficient removal of bone ends up in recurrence of ankylosis while with a wide section a permanent open bite may occur. The authors have reviewed well the different operations so far performed since Esmarch first described it in 1860.

The present tendency is to insert any material which could prevent recurrence of ankylosis—this varies from celluloid fascia, muscle, oxycel, bovine cartilage, etc. A short history of dermal grafts is given, their advantages being adaptability to any surface, superior viability and ready availability in any amount. The absorption rate is only 15 per cent as compared to 30-100 per cent for fat-fascia grafts.

Experimental studies in dogs and monkeys are given with the results and also the results in eight clinical cases—the graft is immobilized over the cut end of the condyle with wire sutures through the bone. Movements of the mandible are initiated from the first day of the operation. Chewing gum is a further aid for masticatory exercise. This procedure assures of an excellent cosmetic and functional result.

#### REFERENCE

Glorgiade, N., Altamy, F., Pickrell, K.: *Plas & Reconst. Surgery*, p. 321, 19, 4, 1957.

*Manibular Retrusion with Ankylosis of the Temporomandibular Joint* : This is a report of 2 unusual cases of some mandibular deformity originating in childhood. The first case was a unilateral underdevelopment of the horizontal and extending rami. Sliding osteotomy and later on bone graft enabled the author to correct the masticatory and cosmetic disability.

In the second case where the temporomandibular joints were ankylosed, an arthroplasty with fascia lata implant between the cut ends was done. Both sides should not be operated at the same time, as the pull of the elevator muscles is likely to close the space between the cut bones. Later on, a sliding osteotomy restored dental alignment, while bone graft restored contour of the mandible. Intraoral skin graft is necessary for retention of denture with sufficient bulk to improve facial contours. The author prefers the use of autogenous bone to foreign body implants.

#### REFERENCE

Kazanjian Varaztad, D.: *Plas., and Reconst. Surg.* p. 91-17-1956.

### Melanomas

*Newer Knowledge of Melanin Pigmentation and the Treatment of Melanin Disturbance of the Skin*: Melanin is formed in the melanocytes of the skin by the action of tyrosine. The quality and the intensity of the reaction may vary with the number of sulphhydryl containing compounds

in the skin, and is influenced by the secretions of the various endocrine glands, by vitamins and other factors.

Melanin formation in the skin can be inhibited by the application of para-hydroxyphenyl derivatives. Melanin formation in the skin can be stimulated by solar or ultraviolet radiation following the ingestion and/or local application of certain psoralen compounds. The monobenzyl ether of hydroquinone can effect depigmentation when applied locally in various ointment bases, and has been used therapeutically in concentrations ranging from 2 to 33 per cent. The medication is applied once or twice daily for weeks or months. The author states that allergic and irritative dermatitis effects are occasionally produced by this compound but can frequently be avoided by using weaker concentrations of the drug. Mercury compounds and ascorbic acid are unreliable depigmenting agents, but may be used to augment the effect of the monobenzyl ether of hydroquinone.

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Knaoff, N. B.: *N. Y. State Med. Jr.*, 55, 3103, 1955.

Scars

*The Treatment of Scars by Shaving and Skin Graft* : The author has devised an operation for scars which are unsuitable for excision and suture—by treating them by shaving with a sharp blade and skin grafting the raw area. It is useful for major scars which would require stage procedures. A matured scar is treated by this method as it has a free capillary circulation and the skin graft takes very easily.

The usual types of scars treated are : (1) unstable scars, (2) scars which are difficult or dangerous to excise, (3) depressed scars, (4) contracted and tight scars, (5) hypertrophied scars and (6) pigmented scars.

REFERENCE

Hynes Wilfred : *Br. Jour. of Plastic Surg.*, p. 1, 10, 1, 1957.

PLASTIC EMBEDDING OF BRAIN TISSUE

V. C. Anguli

An entirely satisfactory process of preserving and mounting brain tissue has eluded museum workers since Vesalius initiated anatomic study of the central nervous system (Circa 1543). Of the numerous technics which have been developed, the most recent and in some respects the most promising is the process of embedding in solid plastic. However, this technic has not been without disadvantages.

It is appropriate, therefore, to review briefly the embedding methods of significance and then to present a suggested technic specifically designed to solve some of the problems.

*Historical Review* : Plastic embedding may be defined as complete encasement of a specimen which is partially infiltrated by one of the transparent resins. The commonly used resins are thermosetting, and the internal temperatures generated by the exothermic reaction of polymerization may be expected to reach 50°C and even 90°C depending on the amount of catalyst, the accelerator, and other factors.

Kampmeier and Haviland<sup>1</sup>, in 1948, pioneered the use of plastic resins in preservation of tissue. Among the specimens prepared by them were slices of brain tissue fixed in 10 per cent formalin and dyed according to the Landau Sincke Berlin method. These brain preparations presented some disturbing factors such as a fluid zone or halo surrounding the specimen, loss of color and disappearance of sharp differentiation between the gray and white matter.

In 1951, Kampmeier and Hospodar<sup>2</sup> experimented with plastic embedding of embalmed cadaver brain tissue. They met with the same difficulties encountered by Kampmeier and Haviland<sup>1</sup> and in addition, the specimens were unsatisfactory because of shrinkage. The bleaching methods used were not capable of counteracting the spotty discolouration in the white matter produced by the diffusion of the blood pigments. The effect of the initial embalming fluid (alcohol-glycerine-phenol) upon the myelin material of the brain was believed to be the chief cause of the discolouration. Their methods are briefly summarized by the following steps : (a) selected sections of tissue were fixed in 10 per cent formalin; (b) the sections were then stained according to Brown's method and the Landau Sincke Berlin method and immersed in a hypotonic syrup for 3 to 6 days

## Plastic Embedding of Brain Tissue

(a procedure designed to minimize shrinkage); (c) the sections were then rinsed to remove the excess of sugar, dried and embedded in a polyester resin containing about 7 per cent styrene. Curing was accomplished at room temperature.

Staining technics, as noted above, have been commonly used in the embedding of brain tissue for two reasons : (a) staining has been the only method of providing gray and white matter differentiation ; (b) differential staining has been used to locate certain tracts and to demonstrate neurophysiologic variation. Procedures for gross staining have been adapted from histological technics but occasionally have met with some difficulty, largely because the stains themselves have not been able to withstand the bleaching action of polymerization.

Kerns<sup>3</sup> in 1953, processed brain tissue in 10 per cent formalin and passed it through 30 per cent and 50 per cent glycerin solutions in 7 per cent and 5 per cent formalin. The final surface dehydration was accomplished in two changes of acetone. An unsaturated polyester resin was utilized as the embedding medium. Stains were not employed for tissue differentiation.

While working in this laboratory, Uills<sup>4</sup> prepared brain tissue by infiltration with polyethylene glycol 600 prior to resin embedding, but the dark colour that glycol characteristically imparts to all tissues, gave unsatisfactory results.

*New Technic* : This technic makes use of the common thermosetting resins, but it involves a method of preparation of the specimen which permits it to withstand the exothermic bleaching action and which provides better gray and white matter differentiation. This is accomplished through the utilization of the distinctive characteristics of glycerine and glycol. Glycerine tends to lighten the colour of tissue while polyethylene glycol darkens tissue. Thus, the basis of this method is the use of the correct proportion of the two compounds in order to obtain an effective compromise. We have been able to achieve good results with fresh tissue and older formalin faded specimens (when a fresh surface has been cut).

1. Preparation and fixation : The brain sections should be cut one quarter inch thicker than desired for the final sections. Fix the sections thoroughly in 10 per cent formalin for a minimum of one week.

2. Dehydration : After fixation the sections are transferred to a glycol-glycerine solution, to be partially dehydrated for 3 to 5 days, the solution having the following formula :

Glycerine	..	..	..	750 ml
Polyethylene glycol (200)	..	..	..	20 ml
Water (distilled) q.s. ad.	..	..	..	1000 ml

At this stage the sections will appear darkened and slightly swollen. Upon completion of the step the tissue is trimmed to the desired thickness.

3. Bleaching: To lighten the colour and restore gray and white matter differentiation, the tissue is now thoroughly dried between paper or cloth towels and then immersed in a bleaching solution having the following formula :

Sodium nitrite	..	..	..	2.5 g
Hydrogen peroxide 3 per cent	..	..	..	50 ml
Water (distilled)	..	..	..	100 ml

The solution should have a pH of approximately 5. The degree of differentiation in the tissue is controlled by the length of time it is kept in the solution, which varies from 6 to 20 minutes. Since the components of this solution are unstable, a new solution should be prepared after 24 hours.

4. Preparing the base layer of plastic: Although the specimen must undergo final surface dehydration in acetone before it is ready for embedding, the time interval of this procedure is so brief and the desired end point so delicate that it is advisable to have a previously hardened base layer of plastic upon which the specimen will rest, in anticipation of the precise moment when embedding may be carried out. This may now be done using an unsaturated alkyd resin with a 33 per cent styrene base. The catalyst, tertiary butyl hydroperoxide, is mixed with the resin in the proportion of 1 drop of catalyst to 2 ml of plastic, and about 100 to 300 ml of this catalyst resin combination poured into a rigid mould with sloping sides (e.g., pyrex refrigerator dish), the final layer after pouring measured approximately one quarter inch in thickness.

5. Final surface dehydration : When this layer has hardened, it is safe to perform final surface dehydration in acetone, perhaps the most critical step in the technic. The specimen should not

be left in acetone longer than 3 minutes, and it may be necessary to remove it before that time depending on the results produced. Experience and judgment are necessary.

6. **Embedding :** After the specimen has been treated with acetone it is placed on the hardened base layer and freshly catalyzed plastic (use the same proportion of plastic and catalyst as for the base layer) poured around it. The plastic stays quite fluid for 1 to 1½ hours and during this time one may remove air bubbles from the specimen with a teasing needle. The superficial portion of the completely poured block will remain incompletely cured unless protected from air. This may be accomplished by using cellophane, a sheet of old X-ray film, or a portion of sheet polyester resin. Unless special procedures are used (heating the block in an oven or exposure to ultra violet irradiation, which we do not recommend), curing for 1 or 3 days at room temperature is necessary before finishing may be performed. When cured, the hardened plastic may be easily released from the dish by tapping the bottom of the mold. The rough uncured superficial layer may be sanded off (if it has not been coated with X-ray film or cellophane) and the block sawed and buffed by using wood working power equipment.

**Summary.**—Various methods of embedding brain tissue have been reviewed. A new method is suggested which employs fixation in 10 per cent formalin and dehydration in a glycerine-glycol solution. Bleaching is accomplished by means of a sodium nitrite-peroxide solution. Final surface dehydration in acetone is utilized prior to embedding the tissue in an unsaturated polyethylene alkyd resin. This method simplifies the process of embedding brain tissue in a plastic resin and assures satisfactory differentiation of the gray and white matter without employing stains.

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## PNEUMOCONIOSIS

K. Venkata Rao

Pneumoconiosis and silicosis once considered as synonymous terms (Kettle, 1934) are no longer considered so in view of the new forms of pneumoconiosis that have arisen in the course of new industries. Thus we can at present recognize many new forms of pneumoconiosis, for example baryllosis (in baryllium workers), bagassosis (sugarcane industries), pneumoconiosis of aluminium workers, of talc in talc workers, etc. These dusts do not affect many individuals. But the high incidence of pneumoconiosis in coal industries has caused great concern all over the world. Much investigation has been done in the direction of finding out the true relationship between silicosis and coal miners' pneumoconiosis. Exposure to coal for a long period gives rise to radiological appearance of deposits without disability and when disability develops it is due to the associated pulmonary tuberculosis. The small percentage of coal miners who develop classical silicosis are the workers engaged in drilling rock, cutting through strata which separate the coal seams.

**Coal miners' Pneumoconiosis.**—A distinction is made between coal miners' pneumoconiosis (without complicating silicosis) and silicosis. In the latter active fibrosis is a feature early in the disease whereas in pure coal pneumoconiosis fibrosis develops after a long period of exposure, when progressive massive fibrosis develops<sup>1,2</sup>. This is believed to be a modified form of tuberculosis in a lung already exposed to coal dust. Thus the pure forms of coal miners' pneumoconiosis can be divided into two categories, viz. simple pneumoconiosis and the other with the associated tuberculous infection. In the early stages of simple coal miners' disease it is difficult to diagnose the condition as there are neither symptoms nor morbidity. The development of late fibrosis ceases at the termination of exposure.

In the simple form coal dust collects around the small bronchioles and their accompanying arterioles and particles are found within the phagocytic cells, having been brought there from the alveoli by these cells. There is no fibrosis. In and around the coal foci the air cells become dilated giving rise to characteristic focal emphysema. This focal emphysema is a characteristic feature of coal miners' pneumoconiosis though this may be present to a slight



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extent in silicosis. This emphysema can be distinguished from the ordinary bullous emphysema by the absence of surface bullae. The accumulated dust acting mechanically causes the emphysema<sup>3</sup>.

It may be said in this connection that accumulation of non-fibrogenic dust in the lungs may or may not show shadows of deposits depending upon the radio-opacity of the dust. Such a condition is described as "benign pneumoconiosis". Iron oxide as found in emery dust or used as a polish in foundry workers produces such a condition. McLaughlin and Harding<sup>4</sup> in a review of lung diseases of 83 patients coming to post-mortem from iron and steel foundry workers found that fibrosis due to dust was present in 90 per cent of cases, but in 40 per cent only this fibrosis was an important factor in the death. The lesions found in the lungs were emphysema and cor pulmonale, tuberculosis, bronchitis, lobar pneumonia, bronchopneumonia and bronchial carcinoma. The pathological changes in the lungs were not only due to siderosis but silicosis and mixed dust fibrosis. The high incidence of carcinoma suggests that there is an increase of this disease among the workers in this industry. Whether it is iron or iron oxide as the aetiological factor is not definitely settled. In the second variety, i.e. the infective variety of coal miners' pneumoconiosis there is fibrosis and this has been attributed to the combined action of tuberculosis and dust. The fibrous masses are dark in colour and frequently contain cavities filled with black inky fluid (cavity due to necrosis, the result of obliterative endarteritis).

In about 40 per cent of these, tubercle bacilli can be demonstrated in the lesions post-mortem. In others it is presumed that the infection has died out. In the past tubercular infection in coal miners was regarded as of low incidence. Such a view is not tenable at present. The infection differs from the usual open type of tuberculosis in that there is no caseation in the lesion in coal workers. There is marked fibrosis and slow progress and the individual dies usually from congestive cardiac failure or from pulmonary arterial thrombosis, the thrombus spreading from a branch of the artery in relation to fibrosis to the large branch at the hilus.

Martin, in a review of four hundred coal miners, admitted to the hospital in the United States over a five year period comes to the following conclusion: "It was found that although disability in general increased with increasing radiological changes there are many exceptions and it was evident that the chest X-ray was worthless as a means of estimating disability"<sup>5</sup>.

**Silicosis.**—The characteristic pathological lesion of silicosis is the familiar silicotic nodule in which fibrous tissue is laid down in concentric arrangement. Free silica (silicon dioxide) is the offending chemical. The toxic action is due to the silica going into solution and acting as a cell poison<sup>6</sup>. If silica is prevented from going into solution by some other substance, e.g. aluminium, the nodules do not form. Kettle (1932) showed that the silica can be rendered insoluble and thereby non-toxic by coating it with iron.

**The Aluminium Treatment of Silicosis:** Denny et al 1939 showed that a similar result could be got with aluminium. The two substances should be brought into direct contact so that the aluminium hydroxide should form a coating to the silica particle to make it insoluble. If aluminium and silica are injected into the trachea in a single dose no protective effect was noted. (Belt and King 1943). King et al (1950) explained this discrepancy due to aluminium being absorbed quickly, leaving silica behind locally to act injuriously leading to fibrosis. Further, they suggest that aluminium should be supplied repeatedly several times a day to prevent silicosis. That the view of mixing of aluminium and other non-fibrogenic dusts with silica prevents true silicosis in this manner is not finally proved at present.

**Caplan's Syndrome.**—In 1953<sup>7</sup>, Caplan described this syndrome of pulmonary silicosis associated with chronic progressive polyarthritis. The opinion at present is that extensive enquiry is needed before polyarthritis can be accepted medicolegally as a complication of silicosis.

**Asbestosis.**—There are two theories in the causation of asbestos pneumoconiosis—chemical and mechanical, the latter being due to asbestos fibres. Trudeau Annual Report (1948) does not support the chemical view. The Saranac workers conclude that asbestosis is caused by mechanical irritation from asbestos fibres during the movements of respiration. The greater incidence of carcinoma of the lung with asbestosis has been mentioned (Report of the British Chief Inspector of Factories, 1947). There is some evidence<sup>8</sup> for believing that carcinoma of the lung is a frequent occurrence in asbestos workers. No such correlation has been found with other forms of pneumoconiosis. No effort to induce cancer in animals exposed to asbestos dust has been successful. Nevertheless the statistical evidence is strong.

**China Clay or Kaolin.**—Kaolin has been found as definitely not responsible for a fibrous silicosis<sup>9</sup>. But others<sup>10</sup> have found severe disability in men working in kaolin industries. Marked pulmonary fibrosis has been found in one case that came to necropsy and in another a nodular type of lesion was found.

**Mica.**—Mica does not produce a true silicosis and though silicosis has been described in the Bihar mica mines this has been attributed to contamination of the dust with silica derived from rock drillings<sup>11</sup>.

**The Role of Mixing Non-fibrogenic Dust with Fibrogenic Dust such as Silica.**—There are some dusts which inhibit the growth of fibrous tissue when mixed with fibrogenic dust such as silica. These dusts may be fixed with comparatively high content of silica and yet do not give rise to the classical symptoms of silicosis. X-ray may show dense shadows but there is no severe morbidity and there is no fibrosis unless complicated by tuberculosis. The above fact probably accounts for the absence of classical silicosis among miners in the quartz reef of the Kolar gold fields.

In conclusion it must be said that no final word can be said with regard to the nonproduction of true silicosis by mixing silica with the so-called non-fibrogenic dusts for there may be other factors involved such as the dilution of silica in the atmosphere, the size of the silica particles, etc.

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**PNEUMOPERITONEUM, PNEUMOTHORAX AND PHRENIC CRUSH**—See ELECTRO-CARDIOGRAPHIC CHANGES IN PNEUMOPERITONEUM, Etc.

#### POLIOMYELITIS, PROPHYLAXIS OF

S. Sen

Though poliomyelitis has been known to exist even from as early as 1500 B. C. the quest for prophylaxis has been a comparatively recent one. Even then, the search for a safe and practical method of inducing active immunity against human poliomyelitis has a long history marked until recently largely by failure. Vaccines made of completely inactivated virus had proved to be too feebly antigenic, while preparations of living virus in mild and supposedly "attenuated" form have proved to be unsafe. Earlier attempts at such prophylaxis resulted in several paralytic infections and as such had to be abandoned. The development of tissue culture on non-neural tissues by Enders and his associates providing a fruitful source of virus without nerve tissue contaminants as was the case in earlier cultures, gave renewed hopes that a safe vaccine could be produced with a high concentration of antigen. The earlier cultures on nerve tissues of infected animals, a meagre source, had the disadvantage of the hazard of homologous tissue sensitization and demyelinating neuropathy. Ender's success gave the impetus and in 1954 Milzer and his colleagues found a method of virus inactivation by ultra-violet light and Salk and his associates could do the same thing with formaldehyde. Both of these gave good antibody responses in animals to all three types of virus. Although it is believed that the former is promising and may have important advantages, the latter, generally known as the Salk vaccine, has been tried on a large scale on human beings.

In 1954 extensive field trials were given to the Salk vaccine as prepared from three virulent strains viz., Mahoney type I, MEF type II and Saukett type III, grown on monkey kidney tissue, inactivated with 1 : 4000 formaldehyde, the formalin neutralized by sodium bisulphite,

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and the final product mixed with merthiolate to a final concentration of 1 : 10,000. Three intramuscular or subcutaneous injections of 1.0 ml were given at intervals of one and four weeks, respectively.

The study was divided into two groups viz., (1) the observed control study, and (2) the placebo control study. In the first, vaccine was administered to children in the second grades, uninoculated children in the first, second and third grades of the same schools being available as controls. In the placebo study, approximately equal numbers of children from the first three grades selected by "blind control" were given the vaccine and placebo. Altogether 1,811,528 children were studied in two groups, of whom 422,743 received complete course of vaccine and 1,388,785 unvaccinated children were available as controls.

The results of the large-scale field trial of Salk vaccine in 1954 on school children were analysed by the Vaccine Evaluation Centre in 1955<sup>13</sup>. Many significant facts were observed in this large-scale field trial; but unfortunately, only the higher figures have been generally publicized, giving both the lay public and the medical personnel a somewhat over-optimistic impression of the efficacy of the vaccine. If one compares all the completely vaccinated children (422,743) with all the unvaccinated (1,388,785) as observed by Faber and Amoss, one obtains paralytic rates of 16.8 and 43.8 per 100,000 respectively, and a protective value against paralysis of 61.6 per cent for the vaccine used in the 1954 field trials.

Other features observed in the evaluation study were, (1) very little protective effect was observed in the six-year group; (2) there was a curiously poor correlation between the antigenicity of the various lots of vaccine and their protective values; (3) no nephropathic effect was noted; (4) the incidence of minor reactions was 0.4 to 0.7 per cent and of major reactions 0.003 to 0.006 per cent, both occurring in approximately equal proportions in both the vaccinated and placebo groups; (5) no paralysis was directly traceable to the vaccine itself.

This appeared to be a very successful result and vaccination was almost immediately instituted in various parts of the United States and within a short period 4,000,000 children received their first shot; soon large stocks of vaccine were prepared by as many as six manufacturing concerns financed by the National Foundation for Infantile Paralysis and released to the market by the Public Health Service of the States. It was soon discovered that the 1955 batches, at least some, could not claim such clean record. There occurred 202 cases of poliomyelitis, three-fourths paralytic, and 11 deaths associated with the vaccine prepared by one manufacturer, of which 79 occurred in vaccinees, 105 among family contacts, and 20 among community contacts<sup>14</sup>. A small epidemic was reported from Idaho attributed to the vaccine. Type I virus, presumably of Mahoney, was recovered from 100 patients, and type II and III on single occasions. Virus was recovered from some batches of the vaccine. A small number of cases was associated with another manufacturer's vaccine. This gave a halt to the prophylactic inoculation; and after some stringent methods of control the vaccination was restarted and no further catastrophe has so far been reported.

It must, however, be remembered that Salk vaccine is in the experimental stage and the exact dosage, schedule interval between doses and the duration of immunity are still unknown.

There are certain problems associated with Salk vaccine immunization. It does not prevent non-paralytic infection and so the danger of cross infection remains. Then again we do not know how long the immunity lasts, how often and up to what age and under what circumstances booster injections should be given; this might well be necessary throughout life. These questions are still awaiting specific answers.

The question of lifelong immunity being conferred by a vaccine with attenuated virus, very much in the same way as a lasting immunity by a single attack of certain viral diseases, including poliomyelitis, small-pox and yellow fever, has been engaging the mind of workers in this field. Koprowski and his associates<sup>4</sup> have isolated a non-paralytogenic type 2 strain with excellent antigenic results. This has been tried on a small group of children. Given orally it produced infection as proved by faecal excretion of virus and high levels of antibody which has persisted for at least three years. Paralysis has not occurred in any instance.

More recently Sabin<sup>9</sup> has isolated strains of all three types with similar properties which have also been tried by the oral route on a few human subjects with good immune responses.

The danger of reversion of the strains of virus to paralyzing forms is a probability which can only be evaluated by long and careful observation.

Stokes<sup>12</sup> suggested the administration of gamma globulin just before or simultaneously with vaccine. Laurent (1953)<sup>5</sup> states that there is some reasonable laboratory evidence that gamma globulin can afford protection against subsequent peripheral inoculation of the virus. Bodin (1952) and Hammon and his colleagues (1952), have reported in a well-conducted trial on the protective value of gamma globulin in human poliomyelitis. They obtained remarkable results and this places prevention of poliomyelitis on the same lines as that of measles and infective hepatitis. The problem is that in case of a prolonged epidemic, repetition of the injections would be necessary and the amount of gamma globulin required might be quite unobtainable. A combination of active and passive immunization may be the method of choice and an ideal solution. More recently gamma globulin as an agent of immunization has received further corroboration. In 1951 and 1952, in certain epidemic areas, 54,772 children between 1 to 12 years of age were given injections of which half were given Red Cross gamma globulin in a dose of 0.14 ml per lb of body weight. From all these and other experiments it appears that Red Cross gamma globulin afforded a significant degree of protection against infection if given early, and against the more severe degrees of paralysis even when given relatively late, but in any event before the onset of symptoms. It seems that the Red Cross gamma globulin has the advantage of possessing antibodies against all three types of the virus having been prepared from pool of blood from thousands of individuals.

These works were mostly carried out in the United States. In the U.K. the Salk method of vaccine as prepared by Glaxo Laboratory is being used. It is prepared from strains of three types of poliomyelitis virus grown on tissue culture and inactivated by formalin; among the safety tests is the injection of the vaccine into cortisone-treated monkeys for the observation of the effects. Monkeys so treated are highly sensitive to poliomyelitis virus. Salk type vaccines are now being widely used in many countries which is a testimony to its efficacy. But no doubt, attenuated poliomyelitis vaccine will be an ideal one. Cox states, "From a practical standpoint the use of living attenuated viruses as immunizing agents is unquestionably the best method for securing long-lasting and safe protection".

Very recently Lepine<sup>6</sup> reported that from the investigations conducted at the Pasteur Institute (Paris) it appears possible to achieve the twofold benefit of harmlessness and prolonged effect by first producing a passive basic immunity with the aid of an inactivated virus. After at least two and at most ten months have elapsed i. e., when the antibody protection has definitely developed, but has not yet lost its effect a vaccine should be administered which contains not an inactivated poliomyelitis virus, but one that is merely attenuated. This vaccine must not display any neurotoxic effect following oral or subcutaneous administration. Good results have been obtained in experiments with chimpanzees, although it has not yet been possible to determine the duration of immunity exactly. The fact that the viruses are excreted with the faeces might nevertheless involve a certain risk for the non-immunized population.

A report of the Medical Research Council of Great Britain, on the assessment of the British vaccine against poliomyelitis has just been published (B.M.J., June, 1957). In their trial on 74,660 children born in 1947-50 who received only two injections, only one developed paralytic poliomyelitis i. e., an attack rate of 1.3 per 100,000. The attack rate in the corresponding unvaccinated children was 8.2 per 100,000. At this latter rate 6 cases would have occurred in the vaccinated group in place of one actually observed.

In 74,024 children born in 1951-54 and aged roughly  $1\frac{1}{2}$ -5 $\frac{1}{2}$  years who received two injections of vaccine, three cases of paralytic poliomyelitis occurred giving an attack rate of 4.1 per 100,000. The attack rate in the corresponding unvaccinated children was 20.1 per 100,000. At this latter rate 15 cases would have occurred in the vaccinated group in place of three actually observed. In both age groups, therefore, the observed incidence of paralytic disease in the vaccinated children was only about one-fifth of the incidence in the unvaccinated. The incidence of illnesses reported as non-paralytic poliomyelitis, however, appeared to be uninfluenced by vaccination.

They used formalized vaccine containing the Brunenders type I, MEF<sub>1</sub> type II, and Saukett type III strains. The virulent type I Mahoney strain was omitted in the British vaccine. Although the number of observations was small there appears to be no doubt that Brunenders strain incorporated in the vaccine conferred protection against type I infections prevailing in the community. Considering the limitations of the experiment the conclusion arrived at was

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that it was not possible to assess with any real precision the degree of protection which was conferred by the vaccine. Since some cases of paralytic disease were observed in the vaccinated children, in the form in which it was given, the vaccine did not offer complete protection. On the other hand it did confer some protection, which was probably quite substantial over the ages  $1\frac{1}{2}$  to  $9\frac{1}{2}$  years. If the small numbers available are taken at their face value the apparent protection conferred was very similar to that observed in 1954 trial in the United States.

Attempts are now being made to produce an oral vaccine which will give immunity to the paralytic form of poliomyelitis. The impetus given by Koprowski et al<sup>4</sup> has stimulated research on this line and in 1957 has produced some papers on this subject. The successful immunization of children with an orally administered attenuated type II polio virus has been described by Koprowski, Norton, Jervis, Nelson, Chadwick, Nelson and Myer (1956)<sup>4</sup>. The virus used was the TN type II rodent-adapted strain. One hundred and fifty children in institutions in the U.S.A. were vaccinated with this virus between 1950 and 1955. Prior to vaccination all children were without antibody to type II polio virus; after vaccination nearly every child (in one series 86 out of 87) developed antibodies. Reasonably high antibody titres were found and persisted in some cases upto five years. No reaction or illness attributable to vaccination were observed. The TN vaccine virus which has been adapted to growth in the mouse central nervous system did not produce cytopathogenic changes when inoculated on to monkey kidney tissue cultures. The TN type II vaccine appeared, so far as could be judged from the laboratory data and the relatively small numbers vaccinated to be both safe and immunogenic. A small trial was recently planned and executed in Northern Ireland to confirm laboratory characteristics of Koprowski's findings. The trial was executed in the following manner. In the first place the vaccine virus as described by Koprowski was confirmed, then a small number of adults (laboratory workers and medical students) were fed with the vaccine. Later a few infants and children of the investigators were vaccinated. Finally the vaccine was fed to a larger group of children. Altogether 21 adults, 10 infants, and 159 children were fed TN type II attenuated polio virus vaccine. The development of antibody was very satisfactory and was associated with the excretion of virus with faeces.

Further, Koprowski et al (1956)<sup>4</sup> have reported the successful immunization of 75 children by the oral administration of SM type I live poliomyelitis virus vaccine. All children whom they vaccinated developed homotypic antibody in response to vaccination and none of them developed any serious illness. The faecal excretion of the virus was considerable and that may constitute a danger to the family. The SM vaccine virus did not cause paralysis in monkeys when inoculated by the intracerebral route. However, it did paralyse monkeys when inoculated intraspinally. The significance of paralysis in monkeys inoculated by these two routes and the reasons for considering lack of intracerebral pathogenicity as a sign of attenuation have been discussed by Dick and Dane in 1957<sup>2</sup>. The SM type vaccine is now being studied with attenuated virus. The TN virus vaccine has the apparent advantage that the faecal excretion of the virus is small, constituting a relative safety to the family.

This opens up a future possibility of a highly potent oral vaccine. Although the TN and SM strains are not at the moment acceptable for mass immunization, this does not mean that suitable strains will not be developed in the very near future. The drawback at present of these two strains of vaccine is that they and the excreted virus are not intracerebrally avirulent for monkeys and that the virus is transmissible from the vaccinated to the non-vaccinated individuals.

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**POLYMYOSITIS**—See MYOPATHIES AND POLYMYOSITIS

**POST-MORTEM LIVER FUNCTION TESTS**—See LIVER FUNCTION TESTS, POST-MORTEM

## POTASSIUM, ITS ROLE IN BODY FLUIDS AND MUSCULAR CONTRACTION

A. Sitaramamurti

**Body Fluids.**—Potassium is one of the elements known to be essential for maintenance of integrity of the mammalian organism. The circulation of potassium in the body can be considered under : (1) transfer between the intra- and extra-cellular compartments and (2) movement of the ion among the several divisions of the extracellular fluids. Howard Holley and Carlson (1955) in their account of potassium metabolism have described the transfer of intracellular potassium to extracellular fluids. Massive haemolytic reactions as in transfusion reactions and haemolytic anaemias, may release abnormal amounts of intracellular potassium and with adequate renal function, the excess of potassium is rapidly excreted. These authors give an account of a patient in whom transfusion with incompatible blood caused severe haemolysis, releasing large amounts of intracellular potassium into the blood plasma of the patient and the simultaneous renal tubular lesion accompanying this reaction would prevent the regulation of the plasma potassium concentrations.

Keynes (1949, 1954), with the aid of radioactive tracers studied the mixing between the intracellular and extracellular electrolytes specially potassium and sodium. The experiments of Hodgkins and Keynes (1953) and Harris (1954) revealed that the exchange of the ions between the cells and the surroundings is slow, and the restraint of the ionic movement must be largely in the cell surface, as the labelled potassium and sodium ions, when they enter the cell, can be seen to diffuse and migrate electrically along the interior with the speed corresponding to that of unrestrained diffusion and conduction in aqueous medium. The source of energy for the propagation of "all or none" impulse is derived from the concentration gradients of potassium and sodium ions across the fibre membrane. Experiments are also in progress for some years (Steinbach, 1954 and Hodgkins and Keynes, 1955) on the problem as to how the nerve and the muscle cells manage to replenish the ionic store and maintain high concentration gradients against the leakages caused by incessant transmission of impulses to and from the central nervous system.

Shaw (1955) studied the intracellular potassium accumulation in erythrocytes using radioactive potassium. The efflux and the influx have been studied separately under different conditions particularly at a variety of external potassium concentrates in the red cells as experimental material of hog, ox and sheep. Streenten and Solomon (1954) have made the measurements of potassium influx in human red blood cells at various levels of external potassium

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concentrations. Frazier, Siclar and Solomon (1954) have made similar studies in the red cells of dogs. In these experiments it was found that the potassium influx increased rapidly as external potassium concentrates were increased to 10 mM and then increased more slowly and linearly with potassium concentrates, indicating that the ions are moving independently of each other, whereas, a limiting rate of influx is to be expected if the ions are carried by a transport system of limited capacity. The potassium efflux was almost independent of the composition of the external medium, but was proportional to the slope of the linear part of the influx concentrate.

Electrolyte changes in transfused erythrocytes were studied by Hal Crawford and Mollison (1955) in red cells stored at 20°C in various citrate mixtures, because of their greatly reduced content of the base. It was found that the cell potassium, cell volume, and osmotic fragility rose slowly after transfusion and normal values were not reached for four days. The rate of gain of cell potassium after transfusion was as expected from the known rate of efflux and influx in normal fresh red cells. The net potassium influx was found to be approximately the same as that of fresh cells which is suggestive that the potassium transport mechanism in stored cells is defective or that the cells are abnormally permeable, as otherwise, the stored cells with high sodium content and raised sodium efflux would have a high potassium influx, as high as twice the normal value. (Flynn and Maizels, 1949 ; Ponder, 1950.)

Anderson and Mudge (1955) studied the effect of potassium on intracellular bicarbonate in slices of kidney cortex and have directly demonstrated that the intracellular concentration of bicarbonate is related to that of potassium, and thus support the hypothesis that the pH of the cell of the renal tubules may directly influence renal excretion in the regulation of the acid-base balance in conditions of potassium depletion or excess. The experiments also indicate that the level of tissue bicarbonate can be influenced by potassium and these effects may be attributable to intracellular changes. The effect of human extracellular pH change on the relationship between the serum potassium concentration and intracellular potassium concentration was studied by Burnell, Villamil, Uyeno and Scribner (1956). They indicate that in the human body, the extracellular pH, changes independently of total body potassium. It was stated that acidosis increases and alkalosis decreases the serum potassium concentration for every tenth unit change in extracellular pH. There was an average inverse change of 0.6mEq/L in the serum potassium concentration. Ionic transfers between extracellular and intracellular fluids were calculated by Elkinson et al (1955) in five normal subjects during and after acute respiratory alkalosis produced by hyperventilation and in another batch of six similar subjects during and after acute acidosis produced by CO<sub>2</sub> inhalation. Direct calculations were made of sodium and potassium transfers. The results indicate that in acute respiratory disturbances, the acid-base equilibrium involves transfer of hydrogen between extra- and intracellular phases of the body fluids and the net transfers of cellular hydrogen were reciprocally related to those of cellular sodium plus potassium. The intracellular potassium exhibited changes that are smaller in magnitude, the mean change being -3.8m Eq and -3m Eq during respiratory alkalosis and acidosis respectively and a significant intracellular potassium was found during recovery period in respiratory alkalosis.

The concentration of sodium and potassium in human sweat were measured after stimulation of sweat with local injection of mecholyl (B-methyl acetyl choline hydrochloride) (Schwartz and Thaysen, 1957). The concentration of sodium rose with increased sweating rate, but was always lower than in plasma. In each batch the concentration of sodium in the initial sample was higher than the concentration of sodium in the sample of the sweat obtained in the following period, and this phenomenon was not observed with potassium.

Ever since the first full statement of the membrane theory (Bernstein, 1912), it is widely believed that the mechanism of nerve conduction depends on certain important differences between the concentrations of the electrolyte inside and outside the nerve fibre. Several authors (Mc Lennan and Harris, 1954) recently estimated the total content of sodium, potassium and chloride in various mammalian nerves and are of the view that the information is still limited by the complete uncertainty about the relative proportions of intra- and extra-cellular fluids and the relative proportions of intra- and extra-cellular sodium, potassium and chloride. By a direct comparison of intra- and extra-cellular areas in photomicrographs of intact nerves of cat, direct estimation of extra-cellular space was made (Kranjevic, 1955). Accordingly the mean value of intracellular area was 43.4 per cent (S. E.  $\pm$  1.3). The intrafascicular extracellular space which includes the myelin sheaths, was 56.4 per cent. Extracellular potassium was found to be



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5-7m.mole/kg water and intracellular potassium 181-183m. mole/kg water. The high content of potassium plus sodium put together amounting to 250m. mole/kg in the extracellular fluid in which the nerves are bathed is of high content as compared with the plasma concentration. This hypotonic concentration of nerve fluids was attributed at least partly to some additional active process in the sheath, in addition to the endoneural protein.

**Muscular Contraction.**--Howard et al (1955) clearly put forth that the potassium ion has a threefold relationship to muscle metabolism, namely (a) that it is concerned in energy production by muscle cells, (b) that it is essential for the mechanism of contraction and (c) that it effects muscle cell irritability. The first two factors are related mostly to the intracellular potassium ion concentration and the last one appears to be related to the concentration of the ion in the extracellular fluids bathing the muscle cells.

Experiments on skeletal muscle are being carried on, for fuller knowledge of the role played by potassium in voluntary muscle contraction. Potassium deficiency or disturbance in the potassium-sodium ratio can lead directly to interference of muscle cell nutrition and hence to muscular weakness with eventual atrophy and necrosis. The muscle proteins (actin and myosin) forming the contractile elements of muscle, require potassium ions for their action. However, it has been shown that in myasthenia gravis, the intracellular potassium content of muscle fibres is elevated whereas, in patients suffering from myotonia and muscular dystrophy, the potassium content is subnormal. The amount of potassium and sodium ions of muscle tissue have been established to be potassium 112mEq and sodium 37mEq per litre of cell water. Various pathological processes involved the loss of cellular potassium with accompanying transfer of sodium ions from the extracellular fluids into the cells and the clinical syndrome associated with potassium deficiency i.e., hypopotassaemia or hypokalemia may produce physical disturbances of serious importance. Majority of the symptoms associated with potassium deficiency syndrome are the result of decreased concentration of potassium in extracellular fluid though it cannot be overlooked that the critical intracellular potassium deficit may account for some of those symptoms.

Katz (1956) states that the membrane of the muscle fibre serves two inter-related functions, viz, it provides a diffusion barrier maintaining a high potassium concentration inside and is concerned with excitation with rapid spread of activity throughout the cell. The membrane is the seat of resting potential. There is evidence that acetyl choline increases the permeability of the membrane and thereby sets up a potential change which is then propagated along the muscle fibre. Acetyl choline was found to increase the electric conductance of the end plate membrane even when all the sodium in the surrounding medium has been replaced by potassium (Castillo and Katz, 1955). Acetyl choline is released in quanta in discrete parcels from the nerve ending and acting on receptors in the external surface of the end plate membrane, causes a large increase in permeability to sodium, potassium and possibly other free ions. This gives rise to local currents of sufficient intensity to depolarise and excite the surrounding area of the muscle fibre and so initiates a new propagation impulse (Katz, 1956). The average resting potential of frog's sartorius muscle in Ringer's solution containing 2.5 mM-KCL is 92.2 mv. and pairs of muscles of same frog appear to have nearly equal potentials than the muscles of different frogs. [The normal internal potassium concentration is  $139 \pm 2$  mM/kg fibre water. At physiological external potassium concentrates greater than 25mEq/L, the membrane potential depends primarily on the ratio of internal and external activities of potassium. At physiological external concentrations of potassium, the membrane potential is not independent of the internal concentration when this is altered by changing the external osmotic pressure (Adrian, 1956)]. The permeability of the membrane to potassium ions has been compared in denervated and normal muscle of frog using  $^{42}\text{K}$  as a tracer ion. Denervated muscle takes up 23 per cent less potassium per g tissue from the outside during the first hour as indicative of a reduction in the membrane permeability (Harris and Nicholls, 1956). A new method of measurement of membrane potential at a single node of Ranvier during rest and activity was described by Stampfli (1956). Addition of potassium chloride solution produces in less than a second, a new equilibrium potential of the membrane close to zero.

Shaw and co-workers (1956) have measured resting action potentials of the sartorius muscle of toad (*Bufo marinus*) under varying conditions of external environment. At the same time, by analysis, sodium and potassium ion level between 0 and 50 m Eq/litre has little influence



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on the internal potassium ion concentration and the maintenance of the normal potassium ion content of the cell cannot be accounted for by a Donnan mechanism.

Natori (1955) induced local and conducted contraction in isolated myofibril, by local application of 1-3M-KCL solution. Conduction velocity varies for about 70 to 700  $\mu$  per second at temperatures from 0 to 20°C. Conduction is with decrement and does not travel further than 1 mm. Combination of sodium chloride and potassium chloride application with electrical stimulation causes repeated contractions, occupying a length of about 10  $\mu$  and travelling over the fibre at intervals varying from 120 to 4 and 10 to 1 second depending on the temperature. The duration of the conduction contraction is 0.2 sec. Overstretched fibrils do not exhibit conduction or repeated contractions.

The potassium content of cardiac muscle decreases in patients dying of congestive heart failure and the deficiency was noted only in the left ventricle in patients dying of left ventricular failure and only in the right ventricular muscle fibres in patients dying of right ventricular failure. It was mentioned that digitalis therapy apparently can alter the potassium content of the cardiac muscle. Toxic doses of digitalis decrease the potassium content of the heart muscle whereas, therapeutic doses have no effect or may slightly increase this cation. It is also indicated that patients suffering from potassium deficiency develop signs and symptoms of digitalis intoxication more readily. Excess of potassium ion in the extracellular fluid will alter the character of the electrocardiogram, particularly, the amplitude of the T wave with wide spread, progressive intraventricular heart block. On the other hand, the elevation in serum potassium and calcium can antagonise the effect of elevated level of potassium giving the normal E. C. G. picture. Udwadia and his coworkers (1957) recently carried out metabolic studies of sodium and potassium in seven subjects recovering from congestive cardiac failure. Their results showed consistent negative potassium balance whereas a slight fall in serum potassium was observed on recovery, probably due partly to the negative potassium balance and partly to retransfer of potassium from extracellular compartment to the cells during recovery.

The role of potassium on plain muscle is indicated in conditions of paralytic ileus and atony of urinary bladder by subnormal levels of serum potassium concentration acting through the autonomic nervous system. Both hypotension and hypertension may result from perfusion of the autonomic ganglia. The inward and outward movements of radio-active potassium were studied by Born and Bulbring (1956) in isolated intestinal smooth muscle preparations (taenia coli of the guinea pig). The rate of uptake of  $K^{42}$  decreases with time (within the first hour, half the final radioactivity was taken up and after three to four hours, a steady state was reached). During the spontaneous rhythmic activity, each increase in tension was associated with increased outward movement of  $K^{42}$ , histamine, and acetyl choline provided an increased rate of outward movement of  $K^{42}$  closely related to tension. Adrenaline did not reduce outward movement but increased the rate of inward movement of  $K^{42}$ .

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## PREDNISONE AND PREDNISOLONE

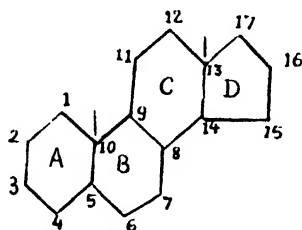
V. Iswariah

Ever since cortisone and allied compounds have been in use for diverse ailments, search for cheaper, less toxic and more effective substitutes has continued. As most of the allied corticosteroids had the common structure consisting of three six-carbon rings attached to a five-carbon ring, chemists had synthesised several compounds ultimately arriving at prednisone and prednisolone.

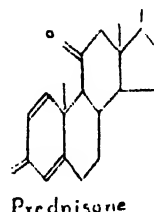
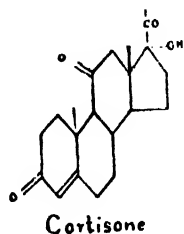
By 1939, six of the steroids isolated from the suprarenal cortex were found to be effective in prolonging the life of adrenalectomised animals. In 1946, a contribution of some importance was made in the synthesis of an active steroid from bile acids as starting point. But chemical synthesis altogether was a long and tedious process, one of the bugbears in the synthesis being the attachment of oxygen to the 11th carbon atom in the steroid structure.

It was then known that only two natural steroids had already this 'troublesome' oxygen in the 11th position. One was sarmentogenin, a glycosidal active principle from *strophanthus sarmentosus*, an african vine, and alpha bufogenin from the skin of some varieties of toads obtained in China and Japan.

Chemistry in the meanwhile had also progressed in the direction of transferring O from C 12 to C 11 (see below).

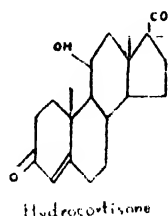


This process has been found simpler than synthesis from bile acids. Today the steroid is obtained from hecogenin, from a sisal plant obtained in large amounts from East Africa (Uganda). The commercial availability led to further researches and the improved cortisone derivatives are prednisone and prednisolone. Earlier named metacortandacin and metacortandrolone, prednisone and prednisolone are analogues of cortisone and hydrocortisone with an important difference (see below).

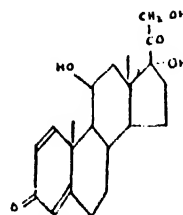


## Pre-Eclampsia

It will thus be seen from the above structural formulae that prednisone differs from cortisone in an unsaturated bond between carbon atoms 1 and 2 in addition to 4 and 5 positions. (Hence also named delta-cortisone.)



Hydrocortisone



Prednisolone

**Action.**—Prednisone and prednisolone are said to be 4 to 5 times as potent as the older analogues<sup>1</sup> cortisone and hydrocortisone but the anti-inflammatory and antirheumatic effects are about equal. Though more potent, qualitatively they are similar, as conditions that do not respond to cortisone are not likely to respond to prednisone. In a comparative study, Dudley Hart and his colleagues<sup>3</sup> noticed that 9 out of 14 patients preferred prednisone to cortisone while 5 were indifferent.

The main difference between the older compounds and prednisone is in the side effects i. e., the new compounds do not cause retention of sodium and water and therefore no hypertension nor oedema. Some physicians<sup>4</sup> have reported a greater frequency of gastric complications and haemorrhage with prednisone and prednisolone as compared to their older analogues.

**Indications :** Broadly speaking, the uses are the same as of cortisone group i. e., collagen diseases like rheumatoid arthritis, rheumatic fever, scleroderma, disseminated lupus; others like nephrotic syndrome, asthma, occasionally blood diseases like leukaemia and thrombocytopenic purpura, haemolytic anaemia; ulcerative colitis and gout also respond to varying extent. They can also be used topically for the eye. In a comparative study for six months by Fisher<sup>2</sup>, prednisolone proved slightly superior to hydrocortisone in 'some respects but statistically insignificant'.

The lack of salt retention confer on prednisone and prednisolone a preference in the treatment of nephrotic syndrome and cardiac or cirrhotic oedema that do not respond to mercurial diuretics. In hypertension and heart failure the new compounds can be preferred.

Prednisone and prednisolone may suppress adrenal function. If the compounds are abruptly withdrawn, there may be evidence of adrenal insufficiency. It has even been suggested that during the use of these compounds, ACTH may need to be administered to keep the adrenals in functioning order or prevent disuse atrophy.

The other complications of cortisone and hydrocortisone therapy like miliary tuberculosis, psychosis, haemorrhage and gastric ulcer, infections like pneumonia and osteoporosis, may be noticed with prednisone and prednisolone treatment. Prednisone in combination with aspirin or amidopyrin is available as proprietary preparations with claims of reduced dosage and toxicity.

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## PRE-ECLAMPSIA

K. Bhasker Rao

The cause of pre-eclampsia still continues to be elusive. After studying the functions of the different organs of the body in normal and pre-eclamptic pregnancies, certain conclusions have been drawn, at least, regarding its pathogenesis. Most important organs involved are the brain, kidneys, uterus and placenta. Due to narrowing of cerebral vessels in pre-eclampsia there is diminished blood flow in the brain. There is a definite glomerular ischaemia in pre-eclampsia as shown not only by renal biopsy studies<sup>1</sup> but also by measurement of the renal plasma flow and glomerular filtration rate (G.F.R.)<sup>2</sup>. During normal pregnancy there is almost a 50 per cent rise in both these values, but in pre-eclampsia, the renal plasma flow as well as the G.F.R. is reduced to half the normal levels. The antidiuretic hormone (A.D.H.) and

steroids act on distal convoluted tubules in pre-eclampsia causing greater reabsorption of water and retention of sodium. Blood uric acid levels<sup>3</sup> also rise in pre-eclampsia as a result of disturbed renal function; further, renal physiology is deranged because of cortico-medullary shunt<sup>4</sup>. Placental functions are also curtailed, and due to infarcts (caused by spasm of decidual vessels), the foetus gets less oxygen. The production of steroids and protective enzymes by the placenta as against A.D.H., pitocin and histamine diminishes, bringing about varying general and local phenomena. Morris<sup>5</sup> has shown by injecting radioactive  $\text{Na}^{24}$ , that there is marked reduction in effective blood flow through the uterus and this is further curtailed by exercise but improved with rest. All this work proves that due to the rise in general vaso-tonus and other factors, there is diminution in the blood flow through the brain, kidneys and the chorio-decidual space.

Imminent eclampsia has been the subject for discussion at the British Congress of Obstetricians and Gynaecologists in 1955. Most of the interesting papers referred to in this subject were presented at the meeting. In imminent eclampsia, the patient has blood pressure over 160/100 mm mercury, widespread oedema, severe albuminuria, oliguria, headache and other warning signs of an impending eclampsia. What exactly precipitates the fits in a severe pre-eclampsia during pregnancy or a mild pre-eclampsia during labour is still not clear. According to James<sup>6</sup> there was no statistical difference in the cerebral dysrhythmia as shown by abnormal EEG in pre-eclamptic and eclamptic women. Morris considers that the convulsions may be initiated whenever the diastolic pressure rises to 100 mm mercury or more and result in cerebral oedema and increased motor irritability in the cerebral cortex. In 84 per cent of eclampsias studied by him, the diastolic pressure was between 100 mm—140 mm Hg.

Treatment of severe pre-eclampsia, especially, in imminent eclamptics is aimed at (i) reducing the vasospasm or blood pressure and to improve the circulation and efficiency of the different organs involved, and (ii) diminution of the oedema. Rest and sedation are still the most helpful procedures. Hypotensives have been used to bring down the blood pressure and also to tide over the crisis as in imminent eclampsia. Ganglion blocking drugs (hexamethonium compounds) have been tried by Townsend<sup>7</sup> and others. They depress the cerebral and renal blood flow, give a transient and variable drop in the pressure and may produce ileus in the mother or the child and therefore are not favoured. Veratrum compounds, by peripheral vasodilatation, produce fall in blood pressure but diminish renal blood flow. Their alkaloids administered orally, however, have given consistently good results in the hands of Kellar<sup>2</sup>. Phthalazine derivatives (Apresoline) given intravenously act on the vasomotor centre to produce fall of blood pressure—increased cerebral and renal blood flow. But they are not powerful hypotensives and are therefore combined with veratrine or serpasil. The effect of all these hypotensives is for a short period only, of 12 to 24 hours; in those imminent eclamptics, at 30 to 33 weeks pregnancy, to tide over the patients for 4-8 weeks, these are useless. Oedema is controlled by restricted salt and water (daily intake of 1500 ml plus the volume of urine passed). Hypertonic glucose intravenously is a good diuretic. Diamox and ion-exchange resins have been also found useful. In imminent eclampsia at or near term with a ripe cervix and engaged head, the bag of membranes is ruptured artificially (ARM) and pitocin drip is given. In a primipara of less than 36 weeks, caesarean section is advisable or a trial with pitocin induction and then ARM may be done, followed by the pitocin drip again—provided, in the meanwhile, that the blood pressure is controlled by sedatives and hypotensives. If pitocin drip does not help in about six hours, caesarean section is the only alternative.

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#### PREGNANCY AND HEART DISEASE

L. K. Ganguli

Proper antenatal care lowers the maternal and infant mortality rates in women with rheumatic heart disease, though there is no doubt that repeated pregnancies hasten chronic invalidism and shorten the span of life. For the assessment of the functional capacity of the heart it is

## Pregnancy, Prolonged

ideal to classify patients from their pre-pregnant state. But seldom patients are seen at that stage. Many patients present themselves for consultation after conception and the majority of them are not aware of the presence of the heart disease until it is revealed during an examination while being pregnant.

Somewhat unusual facts were reported by Laake<sup>1</sup> who analysed 116 pregnant patients with organic heart disease. He found majority of patients developed cardiac decompensation during puerperium. According to him no correlation exists between congestive failure and the number of births and the location of the valvular involvement. Acyanotic congenital heart cases (7 cases studied) are not adversely influenced by pregnancy.

Miller and Metcalfe<sup>2</sup> followed up the effect of pregnancy in 106 patients with heart disease for 3-5 years. From the first observation period of alteration of functional status of the heart to the end of the follow up period there were 3 deaths, worsening of the original status in 11, 65 remained stationary and 27 patients improved. Of these 106 patients, 92 had rheumatic heart disease, 8 congenital heart disease, 1 hypertensive cardiovascular disease and 1 combined hypertensive and rheumatic heart disease. Based on the American Heart Association classification at the start 4 were in an uncertain group, 64 in class I, 19 in class II, 14 in class III and 5 in class IV. Operative procedure performed since pregnancy, was responsible for causing improvement in 6 patients (out of 27). According to them patients with hypertension and mitral stenosis and with combined mitral stenosis and insufficiency or aortic stenosis and insufficiency were the worst cases and died. The authors admit that improvement in the functional capacity might have been due to the fact that the original classification was arrived at during pregnancy. No permanent change to the degree of heart disease could be attributed to pregnancy.

Analysis on the effects of pregnancy before, after and during child-bearing in patients with only congenital malformation of the heart has been done in 53 patients by Espino-Vela and Castro-Abreu<sup>3</sup>. The analysis (see table) was done with reference to tolerance to the malformation itself and the combined effect of the malformation and pregnancy. There were 4 deaths in the series.

TABLE SHOWING CONGENITAL MALFORMATION AND DEGREE OF TOLERANCE DURING PREGNANCY.

Congenital Malformation	Total No. of Patients	No. of cases with tolerance :---		
		Excellent	Good	Poor
Patent ductus arteriosus .. .. .	28	15	4	9
Atrial septal defect .. .. .	13	12	..	1
Coarctation of aorta .. .. .	6	..	6	..
Ventricular septal defect .. .. .	2	2	..	..
Fallot's tetralogy* .. .. .	1	..	1	..
Dextrocardia .. .. .	1	..	1	..
Pulmonary stenosis .. .. .	1	1	..	..
Aortic stenosis .. .. .	1	1	..	..

\*Operated (Blalock-Taussig) at age 19. Pregnancy at 23.

The authors are of the opinion that the tolerance to the malformation itself is the best guide in the prognosis of patients to undergo pregnancy.

**Myocardial Infarction During Pregnancy:** Though very rare, yet is a most important problem involving both the physician and the obstetrician. Antonius et al<sup>4</sup> have recorded such a case bringing the total of such records to 8 cases. They have advocated the use of anticoagulants with caution and the choice of delivery at term *per vaginam* with the aids of forceps. Anticoagulants traverse the placenta and haemorrhage in the newborn has been reported in previous cases.

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## PREGNANCY, PROLONGED

Pregnancy is said to be prolonged when it is carried beyond 294 days after the last menstruation. About 10-12 per cent of deliveries fall into this group<sup>3</sup>. Prolonged pregnancy is a concept of time whereas postmaturity is a developmental or biological state and is not a synonymous

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term. Postdated labour is not affected by age, parity or sex of the child. But there is no doubt that in these cases, the perinatal mortality increases, labour is prolonged and there is a rise in birth weight. Foetal hypoxaemia increases with prolongation of pregnancy, and the perinatal mortality increases with each week beyond term. It is 2.7 per cent at the 42nd week, 6.0 per cent in the 43rd, 9.5 per cent in the 44th and 16 per cent in the 45th week. It is greater in primiparas (6.7 per cent) than in multiparas (1.6 per cent)<sup>2</sup>. But according to Higgins<sup>1</sup>, the higher still-birth rate is met with only if there is associated toxaemia or disproportion. Because of the prolonged labour and rising perinatal mortality, it is advisable to terminate all pregnancies, which proceed beyond 42 weeks, by induction of labour. But if there is an associated toxaemia and disproportion, or if postmaturity is suspected caesarean section is the ideal method of delivery.

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#### PREGNANCY, TOXAEMIA OF

R. K. K. Tampan

Toxaemia is one of the common complications of pregnancy and in every antenatal ward attached to hospitals at least one out of every ten patients if not more, is found to be suffering from this condition. Its high incidence and the complications and sequelae it is likely to lead to, make this disorder one of the major causes of maternal and foetal mortality.

The term "toxaemia of pregnancy" applies to a symptom complex occurring during pregnancy, labour, or puerperium and is characterized by the appearance of one or more of the following manifestations: oedema, albuminuria, hypertension with or without convulsions and coma. In addition, various cerebral, visual, gastro-intestinal and renal symptoms may also occur. It is often the root cause in many cases of maternal mortality though the immediate cause of death may be haemorrhage or infection. The aetiology of this condition, in spite of many attempts at solution, has still remained obscure. Many investigations have been undertaken to study the blood, urine, cerebrospinal fluid and the circulating hormones as also the functions of the placenta, liver, kidney and brain and the role of dietetic principles including the vitamins; but nothing has so far been pin-pointed to indicate the cause of toxaemia.

Tampan and Ramamurthy<sup>1</sup> have dealt with the aetiology of this syndrome, taking into consideration all the available evidence. Since then the following authors have brought to light some more pertinent facts in relation to causation of this problem.

Bartholomew et al<sup>2</sup>, in a detailed study noted that placental infarction and necrosis were a constant feature, to the extent of 80-90 per cent in their cases, in eclamptogenic toxaemia. These are brought about by spasm and occlusion of the placental veins due to the action of oxytocin in the presence of altered hormonal levels (i.e. lowered progesterone, increased free oestrogens and desoxy-like compound). The desoxy-like compound enhances the pressor effect of salt on the blood vessels along with certain other agents. Thus as placental necrosis progresses, the degradation products of nuclear and protein degeneration may become toxic. Their impression after this study is that in all cases of true toxaemia, placental infarction and necrosis should be present and this finding is more suggestive of the cause rather than the effect, as has been believed in the past.

Tampan et al<sup>3</sup> investigating the adrenal cortical functions in normal pregnant, non-pregnant and toxaemic women noted significant increase in the corticosteroid excretion in cases of toxaemia of pregnancy, which return to normal in the postpartum period when the toxaemic condition has subsided. A close relationship in inverse proportion between sodium and potassium excretion ratio and formal dehydrogenic steroid, similar to the relationship exhibited by aldosterone (the recently described, electrolyte-regulating steroid of the adrenal cortex) is demonstrated. The importance of vitamin B complex factors on adrenal function is demonstrated. The mode of production of toxaemic syndrome is suggested in the light of the above findings. The importance of administration of vitamin B complex is suggested before full formation of placenta in order to reduce the occurrence of pre-eclampsia and eclampsia.

Clinical features and diagnosis of this condition are well known and very little has been recently added to them. Much has been done in recent years regarding the treatment of this condition and hence a description of the more recent trends is outlined below.

## Pregnancy, Toxaemia of

Milton et al<sup>4</sup> used sodium pentothal drip originally described by O'donnel Browne in a somewhat modified form and obtained satisfactory results in the treatment of eclamptic convulsions. A freshly prepared solution of 0.25 or 0.3 per cent sodium pentothal in 5 per cent glucose solution i.v., 20 drops per minute as soon after convulsions as possible. Foley's catheter is kept in the urinary bladder which is emptied every four hours, and each specimen measured and tested. The pulse, blood pressure and respiration rate are charted every hour. Oxygen, suction apparatus, laryngoscope, endotracheal catheter and airway are kept handy. Penicillin is given prophylactically. When the convulsions have ceased and the pulse and respiration rate are steady, the concentration of the solution is decreased to 0.15 per cent without altering the rate of flow. When diuresis occurs, the concentration of the solution is further reduced to 0.075 per cent and then slowly cut off when the patient is able to take fluids by mouth. The drip is continued even up to 72 hours. The convulsions are readily controlled by this. Individualisation is the keynote of this treatment and constant attendance by the doctor and nurse is important.

Frank Finnerty Jr.<sup>5</sup> used the purified extract of *veratrum viride* (aqueous injectable Vergitryl), as the principal therapeutic agent in 122 cases of hypertensive toxæmia and found that its intramuscular use produces hypotensive effect in 30 minutes and reaches a peak in 45 minutes, the effect lasting for one to eight hours. Given intravenously, the hypotensive action takes place in one to two minutes but the effect lasts for a variable extent. The chief advantage claimed here is the control of hypertension with concomitant alleviation of toxæmic symptoms, without the use of large doses of sedatives which have a deleterious effect on the premature infant.

Carey<sup>6</sup> reporting on the use of ion-exchange resins in the treatment and prophylaxis of pre-eclampsia states that these resins are valuable agents in oedematous pre-eclampsia, if used very carefully but appropriate steps must be taken to guard against hypokalaemia and the low salt syndrome with the attendant acidosis.

Mayes<sup>7</sup> reported the management of toxæmias of pregnancy with rest, diet, use of magnesium sulphate, intravenous glucose, mercurial diuretics and induction of labour. He considers rest as a diuretic since the kidneys function better when the patient is confined to bed. The main restriction of salt is enjoined. Phenobarbitone  $\frac{1}{4}$  gr is given three times a day if the patient is being observed at her residence. If being treated in a hospital and more sedation is required she may be given one gr phenobarbitone three times a day with  $1\frac{1}{2}$  gr of pentobarbital sodium (one to two tablets at night) and ten gr chloral hydrate on the following morning.

Magnesium sulphate is administered intramuscularly, 5 c.cm of a 50 per cent solution to start with followed by 4 c.cm every four hours till 32 c.cm are given or the blood pressure falls below 140/90. Glucose is given as a concentrated 50 per cent solution, 20 c.cm every two hours for 24 hours. Mersalyl may be used in an occasional case. The delivery is precipitated by stripping the membranes followed by five injections of 3 minim doses of pitocin hypodermically in the case of unripe cervix and by rupture of membranes in ripe cervix. If labour is not brought about in 24 hours, a caesarean section is carried out with penicillin and streptomycin given prophylactically.

Morris<sup>8</sup>, discussing the management of eclampsia, advocates the use of bromethol as a sedative in cases of eclampsia, the average dose being 5.5 c.cm in 223 c.cm of water for a patient weighing 140 lb. It is given by the rectal route. For the restless patient, he advocates the use of pentothal sodium anaesthesia, the patient being brought quickly under the effect of pentothal by a single injection of 0.25 g intravenously, avertin being given rectally before she recovers from the effects of pentothal. The dose of avertin can be repeated when the patient shows signs of restlessness, the second dose being given three hours after the first. Two such doses may be given without any harm except in cases with pronounced oliguria.

Stern and Burnett<sup>9</sup>, evaluating the modern treatment of eclampsia have advanced substantial evidence to show that of the three methods usually followed, namely sedatives by one of the modified methods of Stroganoff's, sedation and control of hypertension by drugs like bromethol or control of hypertension alone by drugs of the *veratrum* group, the last method being the best from the point of view of the mother but as far as the infant is concerned there is very little difference between the use of these.

William D. Cunningham<sup>10</sup>, discussing the method of induction of labour in cases which do not respond to treatment or who in spite of treatment deteriorate due to the toxæmic condition

advocates separation of the membrane in two, three, or more attempts and subsequently when the cervix is ripe, to rupture it, followed by pitocin injection 3 minims every half hour, subcutaneously, upto five injections.

Barry and Quane<sup>11</sup> believe that if some means of reducing the blood pressure during labour could be devised, conservative treatment of toxæmic mothers could be made a relatively safe procedure and the dual dangers of placental insufficiency and eclampsia could be considerably lessened when the blood pressure is maintained within reasonable limits. With this view in mind, hexamethonium bromide was used. Their method was to give a test dose of 10 mg of hexamethonium intramuscularly and the effect of it on the blood pressure was noted. Then 200 mg of this compound is dissolved in a pint of 5 per cent dextrose to which 10 units of hyaluronidase is added. Sub-mammary drip is then set up allowing 20 drops to flow per minute. Frequent blood pressure observations are made and the rate of administration is regulated depending upon the response in the fall of blood pressure. Hexamethonium, besides reducing the blood pressure, also produces relaxation of arteriolar spasm resulting in the immediate disappearance of headache and visual disturbances. The authors are of the opinion that combination of hexamethonium with chlorpromazine is a more potent line of treatment in reducing the blood pressure.

According to Schnieden<sup>12</sup> there is evidence that sodium retention may develop in pre-eclamptic toxæmia. To prevent this, usually a low sodium diet is given but there is a limit to lowering of the sodium intake since when it is below one gram daily, the diet becomes very unpalatable. Ion-exchange resins were given with low sodium diet to prevent absorption of sodium but the quantity of resins required was large and unpalatable. Acetazolamide (Diamox), a sulphonamide derivative and a powerful inhibitor of the enzyme carbonic anhydrase, was used by Schnieden in doses of 250 mg once every third day and observations were frequently made to assess the development of toxæmic symptoms. He came to the conclusion that Diamox was of dubious value, unless accompanied by salt restriction and that it failed completely in some cases. He did not encounter toxic symptoms and in general a favourable impression is created of the use of this drug in pre-eclampsia in patients who begin to put on more than six lb in weight in a month after the 20th week of pregnancy.

Subodh Mitra and Das Gupta<sup>13</sup> report the findings of 133 cases of eclampsia with a mortality of 4.5 per cent which is the lowest they have obtained so far, by methods which they tried in their service, with the use of chlorpromazine (Largactil). The technique adopted was :

- A.1. At 0 hr. 12.5 mg Largactil and 12.5 mg of Phenergan intravenously. In cases where the B. P. suddenly drops or pulse accelerates, 5 to 10 per cent intravenous glucose drips, not exceeding 1½ litre in 24 hours.
2. At the end of one hour 25 mg of chlorpromazine intramuscularly.
3. During the second hour, 50 c.cm of 50 per cent glucose solution with 5 c.cm of 10 per cent calcium gluconate intravenously.
4. During the fourth hour, 25 mg of chlorpromazine and 25 mg of Phenergan intramuscularly.
5. During the eighth hour, 25 mg of chlorpromazine given intramuscularly.
6. During the thirteenth hour, 25 mg of chlorpromazine and 25 mg of Phenergan, i. m.
7. During the nineteenth hour, 25 mg of chlorpromazine, i. m.
- B. Continue O<sub>2</sub> by BLB mask at 3 litres per minute if the patient is anaemic, cyanotic or developing pulmonary oedema.
- C. Venesection in cases of repeated fits and pulmonary oedema when blood pressure is stabilized after an initial fall.
- D. Self-retaining catheter to collect urine every 4 hours.
- E. Artificial rupture of membrane if the patient is in labour and the cervix is ripe and admits a finger.
- F. Low forceps application, or early breech extraction, usually done under sodium pentothal.
- G. Penicillin and Terramycin were used liberally.

This routine is varied to suit the needs of individual cases. In obstinate cases with convulsions sodium pentothal was used; morphia was mostly avoided. No caesarean section was resorted



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to in this series. There was a marked initial fall of blood pressure and acceleration of pulse which in general was stabilised in the course of treatment. There were six deaths in this series which compares favourably with an average maternal mortality of 19 per cent for the last 11 years. The infantile mortality was 39 per cent (58 per cent for the past 11 years). The incidence of obstetric shock was minimised.

Menon<sup>14</sup> reports a series of 150 cases treated with a combination of chlorpromazine, diethazine (Diparcol) and pethidine. This combination was in supercession of his previous line of treatment with a combination of chlorpromazine, promethazine and phenobarbitone. His routine was as follows.

To start with 25 mg chlorpromazine and 100 mg of pethidine in 20 c.cm of 5 per cent glucose intravenously and 50 mg of chlorpromazine and 50 mg of Diparcol are given intramuscularly. A drip of 20 per cent dextrose solution containing 200 mg of pethidine is then set up and this is run in slowly at 20-30 drops a minute. If the patient is quiet, the rate of the drip is reduced. If she is restless, it is increased till the patient is quiet. Not more than 1000 c.cm of 20 per cent glucose and 300 mg of pethidine are given in 24 hours.

0 + 4	hours	Diparcol	50 mg	i.m.
0 + 8	"	Chlorpromazine	"	"
0 + 12	"	Diparcol	"	"
0 + 16	"	Chlorpromazine	"	"
0 + 20	"	Diparcol	"	"
0 + 24	"	Chlorpromazine	"	"

The same schedule of treatment without pethidine is continued on the next day too, chlorpromazine and Diparcol being given alternately every 4 hours in 50 mg doses intramuscularly. An indwelling catheter is kept in the bladder and urine output is noted every hour. Temperature, pulse, respiration rate and blood pressure are recorded every hour. In all antepartum cases of eclampsia if the fits are not controlled by this regime within a reasonable time (8 to 10 hours) pregnancy is terminated either by a caesarean section in those patients with unripe cervix and unengaged foetal head or by artificial rupture of membranes in those with a ripe cervix, the second stage is cut short by forceps.

This regime controlled the fits without recurrence in all mild cases and in 89.1 per cent of severe cases. In nine out of 150 cases, caesarean section had to be carried out due to the inability to control the fits even after ten hours of treatment, the patient being not in labour, cervix uneffaced and the presenting part unengaged. Following caesarean section, no patient had recurrence of fits. The beneficial effects of phenothiazine derivatives in preventing pulmonary oedema, hyperpyrexia, shock and maintenance of good urinary output are emphasized. Maternal mortality was reduced to 2.3 per cent and the foetal to 28.3 per cent. The author emphasises the place of planned caesarean section and the sedative line of treatment in the majority of cases and believes that this combination is responsible for the low maternal and foetal mortality obtained in his series.

Reporting on 733 cases, Mauzy<sup>15</sup> states that in 82.6 per cent cases, pregnancy was terminated by spontaneous labour including those where artificial rupture of membranes was done to induce labour. In 14.2 per cent pitocin was used for induction and in 3.2 per cent caesarean section was done. Induction with pitocin according to him compares favourably with results when labour was spontaneous and if this procedure is properly employed, induction is without risk and yields good foetal salvage. It is most advantageous in cases of premature delivery.

Garber<sup>16</sup> classified the treatment of toxæmia according to labour registration into three main categories, viz., preventive and supportive measures, therapeutic measures and termination of pregnancy. Preventive and supportive measures are education, rest and diet. Therapeutic measures are hospitalisation, sedation with magnesium sulphate intramuscularly and use of vaso-depressor drugs. He used veratrum compounds given by intravenous drips. Veratrum compounds have been used for over 50 years. Two hundred and five cases of eclampsia were treated with an uncorrected mortality rate of 1.5 per cent—corrected mortality being 0.5 per cent.

Assali et al<sup>17</sup> reports the use of Apresoline in the treatment of hypertensive complications of pregnancy; he states that Apresoline given intravenously causes a fall of blood pressure in 10-12 minutes after an intravenous single dose. The diastolic pressure falls sooner and more

sharply than the systolic. Thirty minutes after injection the blood pressure returned to normal and remained so for 4-22 hours.

Menon<sup>18</sup> reported on the conservative treatment of eclampsia in 1150 cases from 1933 to 1950; the average mortality was 15.1 per cent. He gives his impressions of the treatment of eclampsia with sodium pentothal basing his conclusions on treatment of 75 cases with a maternal mortality of 16 per cent and foetal mortality of 40 per cent. He considers pentothal as probably the best medicine for arresting convulsions and preventing their recurrence but it has in no way helped to reduce the maternal mortality. The author feels that sedation and early lower segment caesarean section with a local anaesthetic in suitable cases may help to reduce maternal mortality.

Menon<sup>19</sup> gives data that among 1351 patients with eclampsia treated conservatively from 1938-50, the maternal mortality rate was 15.1 per cent and in 75 cases treated with sodium pentothal it was 16 per cent. He considers that for the patient to survive, causative factor must be removed before irreversible changes are produced in vital organs and for this reason he advocates a planned caesarean section. To begin with, the patient is sedated with  $\frac{1}{4}$  gr morphia and if examination revealed the cervix closed and uneffaced and the presenting part unengaged, lower segment caesarean section was done under local injection anaesthesia. In labour, rupture of the membranes was done and sedation was continued. If convulsions recurred caesarean section was carried out. One hundred and five cases were treated like this among which caesarean was done in 25, one of whom died. The overall maternal mortality in this group was 4.8 per cent and foetal mortality 20 per cent. Caesarean section however is not advocated as a routine procedure for eclampsia.

The nature of antenatal care in the prevention of toxæmia in general and eclampsia in particular has been described by Dixon Hughes<sup>20</sup> of Australia. In a series of patients registered, 20,637 delivered after antenatal care—the incidence of eclampsia was 1 in 5000. The routine followed was to examine the patient as early in pregnancy as possible. Three factors were observed: education of the population to appreciate the results of adequate antenatal care so that mothers are prepared to carry out ordinary common sense hygiene and co-operate with the doctor by regular attendance at the clinic; the staff is vigilant in the out-patient for early signs of toxæmia; proper evaluation of blood pressure. The standard in respect of blood pressure is (1) a rise of 5 mm of mercury in diastolic blood pressure indicated that the patient must be observed within seven days after the twentieth week; (2) if diastolic has again risen within seven days, the patient was re-examined after 2 or 3 days or was admitted to the hospital if other signs of toxæmia developed; (3) if weight increase was associated with a rise of diastolic irrespective of successive weight control, the patient was examined weekly. Presence of albumin in the urine was considered a serious sign. The patient was carefully dieted and instructions were given by a dietitian. The patient was seen in the out-patient as often as the condition of the individual patient warranted it though the routine was monthly examinations up to twenty-eighth week, then fortnightly up to the thirty-sixth week and then weekly up to full term if there were no complications. Results by this method were very good, both in reducing the incidence of toxæmia and also in reducing foetal mortality.

Cosgrove<sup>21</sup> discussing about the management of the toxæmia of pregnancy states that taking the guide in the form of any established knowledge of the aetiology and pathogenesis, the management consists of prophylaxis, treatment of symptoms and termination of pregnancy. The first step is efficient antenatal care during as early a period of pregnancy as possible to detect the early signs of toxæmia and control them. Next step is control of diet, which should consist of high protein and low carbohydrate with plenty of vitamins and very little of sodium. Bed rest is important in established toxæmia. Other measures to control oedema are mild catharsis with magnesium sulphate and diuresis by ammonium chloride given in doses of 8 g for three to four days. Sedatives are necessary in severe cases. Cosgrove's choice in pre-eclampsia is 5 c.cm of 50 per cent magnesium sulphate every six hours with a barbiturate at bed time. Glucose administered intravenously overcomes hypoglycaemia and protects the liver from deprivation of glycogen. The present concept of pathology of toxæmia states the importance of vasopressor action and hence the use of vasodepressant agents are indicated. These agents are substances like alkaloids of veratrum, pthalazine products like Apresoline, and preparations of Rauwolfia serpentina, Priscoline and Divenamine, etc. These drugs are mostly useful in convulsive cases or for those with unusually high blood pressure. If there is response,

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the patient may be observed and labour allowed to commence in time. If the foetus is premature, this treatment may give a chance for foetal survival by prolonging its intrauterine existence. If in spite of treatment, there is no response in 48 hours or becomes worse, termination of pregnancy is resorted to by castor oil orally, stripping the membrane and a pitocin drip. If the patient is not suitable for induction, caesarean section is resorted to under local anaesthesia. If eclampsia intervenes sedation is intensified by the use of magnesium sulphate 2 g in 20 c.cm of distilled water repeated at intervals of one to four hours. A single dose of  $\frac{1}{4}$  gr morphine may be employed. Good nursing care, oxygen inhalation, proper air-way and postural drainage are necessary measures. Low forceps under pudendal block is advocated if second stage has to be helped out. During 1953 and 1954, there were 1851 cases of toxæmia including 13 cases of eclampsia at the Margaret Hague Hospital and they were treated without any maternal death and less than 5 per cent total foetal loss, under this regime.

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## PRESBYCUSIS

J. V. DeSa

The effect of advancing age upon the end-organ of hearing is characterized by two types of changes in the cochlea :

1. Epithelial atrophy ;
2. Neural atrophy.

Presbycusis that results from 'epithelial atrophy' is identified by the degenerative changes beginning in the basal coil of the cochlea and later on proceeding to the apex. The neural type of atrophy shows degeneration of spiral ganglion cells and often it is superimposed upon by epithelial atrophy.

The onset is late in life and the condition progresses steadfastly towards high tone deafness with severe loss in auditory discrimination. The condition is identical to senile dementia where the neurone population of the cerebral cortex is affected by degeneration.

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## PSITTACOSIS

D. Jaganatha Reddy

Kaul and Datta claim that the case of psittacosis reported by them recently from Poona is the first in India. The infection according to them appears to have been transmitted by fowls and they suggest that bacteriological investigation of poultry may disclose reservoir of the psittacosis virus other than that in parrots.

A male patient aged 45, was admitted to the Military Hospital, Poona, for fever, dry cough, severe headache and pain in the right side of the chest. A number of serological tests and cultures for Gram-negative intestinal pathogens, Q fever, influenza, etc. were negative. Skiagram of the chest showed an opacity of uneven density over the right lower lobe, obliterating the right

cardiophrenic region. Repeat pictures revealed progressive but incomplete resolution of the opacity. The spleen was palpable on the 14th day of the fever and a rash was observed.

Complement fixation test for psittacosis and lymphopathia was positive, 1: 32. Response to chlortetracycline was good. The clinical, skiagraphic and serological findings were typical of psittacosis. The authors suggest that clinical findings simulating atypical pneumonia, if investigated for psittacosis, may point to many more cases.

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PSYCHONEUROSES, CARBON DIOXIDE THERAPY IN

N. S. Vahia

At present there is some difference of opinion regarding the value of carbon dioxide therapy in the treatment of psychoneuroses and psychosomatic illnesses.

Meduna<sup>5</sup> advised the use of carbon dioxide therapy in certain types of psychoneuroses and psychosomatic illnesses in his book on carbon dioxide therapy (1950). He has suggested the following method. The patient is made to relax on a bed in a lying down posture. He is made to inhale a mixture of 30 per cent carbon dioxide with 70 per cent oxygen, till he becomes unconscious. The number of inhalations varies from patient to patient, but an average patient requires 20—40 inhalations. When the patient becomes unconscious, his breathing is rapid, the reflexes are affected and the twitching of the hands and feet is sometimes noticeable. When the patient is already unconscious, the mask is removed from his face and after a while he regains consciousness. Some patients become confused or restless for some time after the treatment, but almost as a rule, their mind becomes clear after half an hour. The treatment is given every day and an average patient is given about 30—100 treatments. As some patients feel apprehensive of this therapy Meduna<sup>6</sup> has advised the use of nitrous oxide anaesthesia prior to the administration of carbon dioxide in his later publication.

Meduna postulated that incessant reverberation of continuously reverberating circuits in the brain would be decreased and finally terminated and pathological basis of psychoneurosis eradicated by this treatment. Meduna believes that there are probably many reasons for improvement in psychoneurosis like increased cerebral inhibition, decreased excitability of the cortex, effect of carbon dioxide on carbohydrate metabolism and the changed balance of activity of the pituitary, adrenal and the thyroid glands. In other words, he presumes that there is probably hyperirritability and some disturbances in the interaction of at least three glands, viz. the pituitary, adrenal and thyroid, which are rectified by the action of carbon dioxide.

La Verne and Herman<sup>4</sup> modified the technique of Meduna. In his rapid coma technique he advised the use of higher concentration of carbon dioxide (70—80 per cent carbon dioxide in oxygen). Various techniques suggested are (a) single breath technique, (b) single breath technique with voluntary breath holding, (c) multiple breaths, rapid coma technique preceded by nitrous oxide anaesthesia. He treated 20 per cent of the patients with simultaneous psychotherapy. 133 patients were treated either with Meduna technique or with rapid coma technique. Clinical results of rapid coma technique were superior to those of Meduna technique. Compared to 22 per cent improvement of neurotic group, 50 per cent improved with this technique. There was no significant influence on overall results of the concurrent psychotherapy. He stressed that as carbon dioxide therapy was not without any risk, it should be administered only by a physician.

Moriarty<sup>7</sup> evaluated the results of carbon dioxide treatment in 290 patients (7500 treatments). He considered that carbon dioxide narcosis was an important treatment method for various neuroses and psychoneurotic conditions, particularly when integrated with psychotherapy.

Arthurs et al<sup>1</sup> studied 14 patients with stammering. Evaluation by patients themselves six months after the treatment showed that no marked improvement was noticeable, but speech anxiety was somewhat reduced.

Harris<sup>2</sup> compared the results of treatment with carbon dioxide and psychotherapy. Two groups of 38 cases each, well matched according to mental state, age, sex and duration of illness, followed up for 12 to 15 months after treatment showed no significant difference between the two groups.

## Pulmonary Arteriosclerosis, Primary

Hawkings and Tibbetts<sup>3</sup> showed that regular attendance in a hospital under certain conditions produces improvement in a large number of neurotic patients. In his group of 79 patients more than 50 per cent of those that completed carbon dioxide treatment showed some improvement. In a control series of 25 patients treated with carbon dioxide and other 25 receiving compressed air, there was no distinction. It was concluded that it was the regime and not the pharmacological action of carbon dioxide, that was responsible for this improvement. In their opinion carbon dioxide treatment had apparently no specific therapeutic effect in the treatment of psychoneurosis.

Thus it seems that there is no uniformity of opinion regarding the technique or the value of this therapy. More work will have to be done before its exact indications, most satisfactory technique and its therapeutic efficacy have been established. But the impression is that the enthusiasm created by Meduna's publication has decreased.

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## PULMONARY ARTERIOSCLEROSIS, PRIMARY

D. Jaganatha Reddy

Primary pulmonary arteriosclerosis is an infrequent condition. Only about 40 cases have been reported so far. A diagnosis of the same is acceptable only when at necropsy other causes for vascular sclerosis are not spotted. MacCullum, Killingsworth, Seeley and Branwood have stressed the rarity of the condition in autopsy material. Mehrotra et al recorded full details of a case observed at necropsy from this country. Bhaskara Reddy and C. R. R. M. Reddy while reporting the clinicopathological findings in one case observed that it formed the solitary case of rightsided heart failure registered at the Pathology Department, Andhra Medical College. The case was treated for mitral stenosis for a year and diagnosed from the presence of soft systolic murmur at the apex and accentuated second pulmonary sound. At autopsy conspicuous thickening of the pulmonary artery, sclerosis of the arterioles and thrombi in different stages of organisation were noticed in sections of the lungs. The heart was hypertrophied but was devoid of valvular lesion. The authors do not attribute any causal significance to the occasional thrombi in pulmonary vessels.

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## PULMONARY EOSINOPHILIA

M. V. Chari

Tropical pulmonary eosinophilia is a condition peculiar to India and is seen to a less extent in Burma, Malaya and other tropical countries. Originally it was confused with Loeffler's syndrome, which is a migratory phase of ascariasis. Tropical pulmonary eosinophilia was first described in 1940 by Frimodt Möller and Barton, and later in 1943 by Weingarten. Weingarten also observed the beneficial effect which followed the administration of arsenic to these cases, which were once confused with bronchial asthma. Chaudhuri has drawn attention to a paper published by Roy and Bose in 1919 in the Calcutta Medical Journal describing cases of asthma with leucocytosis and high eosinophil count, responding well to intramuscular administration of Soamin. The credit for describing tropical pulmonary eosinophilia for the first time should, therefore, go to Roy and Bose.

**Clinical Features:** The disease usually occurs in the age group 15 to 40 years. Similar illness in other members of the family may be present. Most of the cases of tropical pulmonary eosinophilia come with the symptom of cough. Asthmatic attack is a symptom seen in a few patients. Others complain of dyspnoea. Fever may be present in a small percentage of cases and is usually of a low grade. The constant auscultatory finding in these cases is rhonchi heard over both the lungs. Haemoptysis is a feature occasionally seen.

Tropical pulmonary eosinophilia is usually diagnosed by the finding of a high eosinophil count. It must be emphasized that the average eosinophil percentage in a country may vary from place to place. The author pointed out in his report to the Indian Council of Medical Research that a percentage of above 20 occurred in 16 out of 100 healthy individuals whose blood was taken during a routine health check-up carried out at a medical exhibition in Mangalore. The arbitrary figure of 20 per cent and above eosinophils in a differential count, or 2000 and above total eosinophils per c.mm as calculated from a total and differential white cell count (or more accurately by using the Hinklemann's method), is accepted as diagnostic of tropical pulmonary eosinophilia. But it must be emphasized that a peculiar feature noted is that cases with high eosinophil count, viz. above 50 per cent may be entirely asymptomatic. In other cases, a relatively low count of 30 per cent may produce severe paroxysms of cough. Another feature observed is that a patient may develop severe asthmatic attacks—even status asthmaticus—and yet his blood count may not show any further increase in the eosinophils. Similarly, a case whose asthmatic attack is controlled with aminophylline or adrenaline may, after the control of the attack, still have the same eosinophil percentage as prior to the attack. In short, the development of severe paroxysms of cough or of asthmatic attacks bears no relation to the circulating eosinophils.

Blood sedimentation rate is raised to 20 mm or more in most of the cases. The sputum does not show acid-fast bacilli, but may show increased number of eosinophils. Helminthic infestation (ascariasis, thread worm and ankylostome infestation) is seen in about 40 per cent of cases. The eosinophilia has no relationship to the helminthiasis, because it may persist even after the treatment of worm infestation. Bone marrow study shows a rise in the eosinophils in most of the cases. Blood culture was done by Neogi. A fungus belonging to the genus streptomyces was isolated in three cases, but was found to be nonpathogenic and a contaminant. Chaudhuri isolated a spirochaete in 16 out of 18 cases from the samples of bowel mucus. But this was also obtained from other non-eosinophilic cases. Chari described a case of eosinophilic granuloma of the breast in which a biopsy was done. The section revealed a preponderance of eosinophils. The lump in the breast disappeared with treatment with urea-stibamine. Biopsy from nodules from one patient and abscess walls in another similarly showed a grouping of eosinophils in the nodules and in the abscess wall.

Liver biopsy was done by Chaudhuri on five patients and showed cellular, mostly eosinophilic, infiltration along the portal tracts in addition to the large number of eosinophils in the sinusoids. This observation was not confirmed by the author in all cases. Gault and Webb in 1957 described in a preliminary report that the needle liver biopsies in 4 children suffering from tropical pulmonary eosinophilia showed "a very striking cellular infiltration, chiefly eosinophils, in the portal tracts". In March, 1957, laparotomy was performed in a case. It was noted that the liver was enlarged, "smooth and homogenous except for two areas where small whitish patches, one to two millimetres in diameter, about a dozen in all, were seen on its anterior surface. . . . . everywhere the portal tracts were widened by a massive cellular infiltration consisting almost entirely of eosinophils. . . . . The anterior end of a nematode larva was also seen in the sections". Gault and Webb suggest that invasion of the liver by nematode larvae and a similar invasion of the lungs is probably the cause of tropical pulmonary eosinophilia.

**Radiological Findings:** These vary with the severity of the symptoms and with different cases. Increased bronchovascular markings may be the early radiological finding. This is followed by fine mottling over both lung fields (which may be called "fine net-work appearance"). In more severe cases the mottling may be more pronounced, giving an appearance which may be similar to that of miliary tuberculosis. Patch or patches of consolidation may also be seen and such cases may be wrongly diagnosed as pulmonary tuberculosis. The author has recently seen one such case treated in a tuberculosis sanatorium with 65 g of streptomycin. Putting the patient on Hetrazan and Carbarsone brought the high eosinophil count to normal in

## Pulmonary Eosinophilia

15 days' time, with amelioration of all the symptoms, and complete clearing of the mottled opacities.

**Pathogenesis :** The pathogenesis of tropical pulmonary eosinophilia is still not definite. Carter in 1944 described mites to be the cause of tropical pulmonary eosinophilia. But this has not been confirmed by subsequent observers. Beaver and his colleagues in 1951 suggested that the invasion of the internal organs by larvae of animal ascarids—*Toxocara canis* and *T. cati*—was the cause of chronic eosinophilia in children in New Orleans. Gault and Webb believe that a nematode larval invasion is the cause of this illness (*vide supra*). Allergy and infection by organisms have also been blamed. What is it that causes an accumulation of eosinophils in the lungs is still not clear. Loeffler produced eosinophilia by injecting daily large amount of vegetable oil and suggested that it was due to allergy. Similarly, Epstein produced eosinophilic pneumonitis in 7 out of 1000 subjects by injecting them with an allergen. It was suggested that "viscera, particularly the lungs, have a tendency to trap or filter out the eosinophils in some unknown way, possibly because eosinophils have an affinity for structures with high histamine reserves, of which the lung is supposed to be one. . . . In the person destined to develop eosinophilic pneumonitis, this mechanism is overwhelmed—perhaps eosinophils crowd in enormous numbers and cannot be disposed of, leading to inflammatory responses". Working on this hypothesis, the author caused a sudden fall in the eosinophil count and noted the corresponding radiological change, if any, which occurred with the fall. For this purpose he took advantage of the clinical observation that a rise in temperature due to infection causes a fall in the eosinophils. By artificially creating such a rise in the temperature viz., by the injection of T.A.B. vaccine intravenously, it was possible to cause a fall in the eosinophils. Such a fall may be due to two factors : (a) it may be due to the destruction of the eosinophils ; if this is so, then side by side with the fall in the peripheral circulating eosinophils, one would expect a fall in the eosinophils trapped in the lungs and in the viscera. In this eventuality one could expect a rapid clearing up of the radiological picture following the fall in the circulating eosinophils. If, however, only the eosinophils in circulation are destroyed, whilst those in the tissues are spared, it is possible that the radiological appearance may not change at all ; (b) a fall in the peripheral eosinophils following shock therapy (T.A.B. vaccine) may be due to the escape of eosinophils from the blood into the tissues including the lungs. In such a case one could expect an increase in the lung shadows following such a fall. In actual practice, it was noted by the author that the radiological appearance took a long time to return to normal, in spite of a rapid fall in the eosinophil percentage. Using cortisone, prednisone or prednisolone a similar fall in the eosinophils can be obtained and the radiological appearance remains unaltered in spite of the amelioration of symptoms and fall in the eosinophil count.

**Treatment :** Arsenic has undoubtedly a remarkable effect in tropical pulmonary eosinophilia. Unfortunately, it is a dangerous drug to use. Arsenic often causes loss of consciousness due to encephalopathy, toxic symptoms like dermatitis of the exfoliative type, agranulocytosis, nausea and vomiting etc., particularly when used in relapse cases. Moreover, it is a well known observation that relapses occur after a varying period and the relapses do not respond to arsenic therapy so well as did the first attack. Cortisone, prednisone and prednisolone bring down the count rapidly. But the effect is only temporary. Emetine may be of use in cases of tropical pulmonary eosinophilia complicated with amoebiasis. Aureomycin has been reported by Chaudhuri in Calcutta and Rao and Krishnan to be of value. But this has not been confirmed by others.

Diethyl carbamazine (Hetrazan, Banocide) in daily doses of 12 to 16 tablets (50 mg each) for 7 to 10 days is said to be effective. In the author's opinion the combination of this with Carbarsone (250 mg) 1 tablet b.d. for 10 days is still more effective. In spite of the beneficial effect claimed by many workers, it is the experience of others that a few cases do not respond to piperazine. Such cases, however, may respond to arsenic therapy. The author recently tried piperazine adipate (Entacyl, B.D.H.) to note how it compared with piperazine citrate. While the citrate preparation acted well in tropical pulmonary eosinophilia there was less response to the adipate compound. The absorbability of these compounds into the blood from the intestines may be the deciding factor regarding their effectiveness. Entacyl is absorbed only to a slight extent from the gut (personal communication from B.D.H.)

## Pulmonary Eosinophilia, Some Unusual Changes

and hence although it is of value in helminthiasis, it is not of so much value in tropical pulmonary eosinophilia. Further work has still to be done in this direction.

The author has used intravenous T.A.B. vaccine to cause a fall in the eosinophils (*vide supra*). The initial dose given was 5 million bacteria, later increased to 10 million, diluted in 10 c. cm glucose repeated every 4 to 7 days. The total number of injections required is six. Such injections cause a rapid rise in the temperature with a fall in the eosinophils. This is a line of treatment well worth following.

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## PULMONARY EOSINOPHILIA, SOME UNUSUAL CHANGES D. Jaganatha Reddy

Frimodt Möller, Viswanathan and Misra drew attention to the existence and increasing incidence of tropical eosinophilia in India. Interesting observations are reported by Misra and Prakash who pointed out that eosinophilia was associated with clinical manifestations suggestive or typical of affection of organs other than lungs and in some cases inclusive of lungs. In all the seven cases reported, eosinophilia was a constant finding and the symptoms cleared only on administration of some preparation of arsenic (see table below).

No.	Sex	Age	Clinical Diagnosis	W. B. C. count per c.mm	Eosinophils	Remarks
1	M	38	Nephritis .. ..	40,200	80 per cent	Responded to neoarsphenamine
2	M	32	Loss of weight and the patomegaly	16,900	46 ..	Responded to Mapharside
3	M	20	Low grade fever for two months	25,400	65 ..	Fever came down with Mapharside
4	M	32	Diarrhoea .. ..	..	4000 per c. mm blood.	Responded to neoarsphenamine
5	M	16	Status asthmaticus .. ..	40,100	82 per cent	Responded to Mapharside
6	M	22	Dry pleurisy .. ..	14,600	36 ..	Cleared with neoarsphenamine
7	M	24	Congestive heart failure simulating rheumatic heart disease	19,000	64 ..	Expired

The disseminate visceral lesions in tropical eosinophilia are now being increasingly recognised. Pickup and Riley reported a case of tropical eosinophilia with acute nephritis who responded satisfactorily to neoarsphenamine therapy. In case 7 listed in the table, gross and histological evidence of rheumatic lesion was wanting but instead focal collections of plasma and round cells and eosinophil cell collections were noticed. Jhatakia described anginal pain associated with eosinophilia and the dramatic disappearance of the same with arsenotherapy. Zuelzer and



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Leonard observed disseminate visceral lesions in extreme eosinophilia in children besides pulmonary infiltrations. He stressed the presence of joint and myocardial lesions and affection of the nervous system. Hepatomegaly associated with liver cell necrosis and eosinophil cell collections progressing to fibrosis in cases of tropical eosinophilia, are being recognised by the pathologist and the clinician. Recently in a young female patient with eosinophilia, observed by us, liver biopsy showed focal collections of histiocytes and eosinophils with early fibrosis. In addition we found close to these cellular infiltrates diamond-shaped, vacuolated areas in haematoxylin-eosin sections. The exact nature of these is being studied further.

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## PULMONARY FUNCTION TESTS

H. D. Singh

The rapid development of pulmonary function tests in recent years has not only advanced our knowledge of pulmonary physiology and pathophysiology but has proved to be of value to the clinician in the management, diagnosis, and in determining the prognosis and the therapeutic procedures to be undertaken in patients with respiratory disability. Numerous tests have been evolved to study the three main aspects of pulmonary function—ventilation, perfusion and diffusion. A monograph by Comroe and his colleagues<sup>8</sup> gives a clear and concise account of pulmonary function tests and their principles, their utility and limitations, and a few case illustrations show their diagnostic value. In another monograph on pulmonary emphysema<sup>20</sup> a chapter is devoted to respiratory function tests, and one of the authors, Meneely<sup>19</sup>, gives a very practical summary of the methods and uses of these tests. A vast amount of literature has appeared on the subject in the last few years. This brief review will be restricted to new data and developments in methods and techniques and the clinical uses of the conventional tests.

**Normal Standards:** In the last decade or so, normal standards for healthy subjects have been determined by various investigators in Western countries. In Indian subjects Thompson Wells<sup>27</sup> has presented data based on respirometric and bronchspirometric studies, and Bhargava and Somnath<sup>5</sup> have correlated Maximum Breathing Capacity (MBC) with body surface area. Singh and Prabhakaran<sup>25</sup> determined Vital Capacity (VC), Timed VC, MBC and MEP (Maximum Expiratory Pressure) in healthy children and adults. While the VC values are lower in Indians, MBC appears to be within the range observed in Western subjects. Data for ventilatory functions in Chinese subjects is given by Wu et al<sup>30</sup>.

**Methods and Techniques:** A simple device based on the Venturi tube principle has been developed for the clinical measurement of breathing capacity; the instrument (a ventube) is compact and portable and can be used easily both by the physician and the patient<sup>28</sup>. Shephard<sup>22</sup> who determined MBC with an improved pneumotachograph and compared the results with those obtained by other methods, recommends that the MBC test should be replaced by the fast VC test in patients who are not very fit. The use of simple roentgenological procedures for the evaluation of ventilatory function is being developed<sup>3,6</sup> and a method of calculating Total Lung Capacity from a single postero-anterior X-ray film of the chest in full inspiration has been described<sup>15</sup>. A formula based on height and tidal air for the prediction of pulmonary dead space has been evolved and recommended for routine use<sup>4</sup>. A body plethysmograph has been employed to determine airway resistance<sup>9</sup>. Mellroy and Eldridge<sup>18</sup> have described two simplified methods of measurement of mechanical properties of lungs. By collection and analysis of air samples taken from the bronchi and trachea during bronchoscopy, information indicating ventilation and perfusion of individual lungs has been

obtained<sup>1</sup>. A method of assessing ventilation of individual pulmonary lobes by breathing a mixture of oxygen, inert Xenon and radioactive Xenon 133, and measuring the distribution of radioactive gas over symmetrical lung fields, has been devised<sup>11</sup>. The latter two procedures do not involve the complex bronchspirometric technique. A rapid infra-red CO<sub>2</sub> analyser has been used to determine mixed venous CO<sub>2</sub> tension by rebreathing<sup>7</sup>, and a direct-writing ear oximeter has been employed to record changes in arterial oxygen saturation in normal subjects and patients with pulmonary disease<sup>29</sup>.

**Clinical Observations :** Gaensler et al<sup>12</sup> have assessed the prognostic value of pulmonary function studies in relation to operative mortality and post-operative disability in pulmonary tuberculosis ; they consider that MBC and TVC as routine tests and bronchspirometry as a special test are of the greatest value. The extent of impairment of ventilatory function which follows thoracoplasty, segmental resection, lobectomy and other surgical procedures for pulmonary tuberculosis has been investigated by Little<sup>16</sup>. Ventilatory function and bronchspirometric studies on some tuberculous patients in South India were conducted by Thompson Wells<sup>27</sup>. Ventilation and gas exchange studies before and after pleural decortication indicate that this operation is followed by functional improvement<sup>24</sup>. In the management of bronchogenic carcinoma the importance of preoperative function studies especially simple spirometric tests, have been stressed<sup>11</sup>, and the alterations following pneumonectomy discussed<sup>17</sup>. Based on the observations that resection for bronchiectasis is followed by significant ventilatory impairment. Smith et al<sup>26</sup> suggest that the choice of therapy should be made only after a careful functional evaluation. Effects on lung volumes and ventilation resulting from thoracotomy for localized pulmonary disease have been discussed<sup>13</sup>. Siebens et al<sup>23</sup> found varying degrees of functional impairment in pulmonary cystic disease and that excision was followed by improvement even when hypoxia was present. It has been suggested that determination of some mechanical properties are more important than conventional function tests for the early recognition of emphysematous changes in the lungs<sup>2</sup>, and Ebert<sup>10</sup> discusses the clinical significance of elastic properties of the lungs. Valvulotomy for mitral stenosis was shown to be followed by functional improvement even when a low preoperative diffusing capacity was present<sup>21</sup>.

The present position is that while some of the tests are simple and suitable for routine use in the clinic, others are too complicated for this purpose and are at present restricted to the laboratory. The tests give information regarding the type and degree of functional impairment, but do not indicate the site and nature of the pathological lesion. In spite of their limitations they are of considerable value as supplementary aids to routine tests and have come to occupy an important place in the clinician's armamentarium of diagnostic procedures for cardio-respiratory disorders.

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## Pulmonary Heart Disease

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## PULMONARY HEART DISEASE

J. C. Banerjee

McGinn and White (1935) first introduced the term *cor pulmonale* for pulmonary heart disease to denote right ventricular failure due to pulmonary embolism. The term is now more commonly used to denote cardiovascular disturbance caused by diseases of the lung parenchyma (Wood, 1956).

**Aetiology:** *Cor pulmonale* is more common in men than in women (5:1). Majority of the cases are above 50 years of age.

Pulmonary emphysema is the classic and commonest cause of *cor pulmonale*. Emphysema may be either primary, or secondary to diseases like chronic bronchitis, bronchial asthma, bronchiectasis, pneumoconiosis, chronic fibrocaceous tuberculosis or kyphoscoliosis.

**Pathologic Physiology:** Wood (1956) stressed two fundamental factors. (1) *Hypoxia*. It is primarily due to emphysema but often aggravated by infections such as bronchitis or bronchopneumonia, which interfere with the filling of sufficient number of alveoli by fresh air leading to lowering of oxygen tension and retention of carbon dioxide. Hypoxia may also be due to thickening of the boundary zone between capillaries and alveoli. As CO<sub>2</sub> is more diffusible than O<sub>2</sub>, there is a tendency to increased CO<sub>2</sub> content of blood.

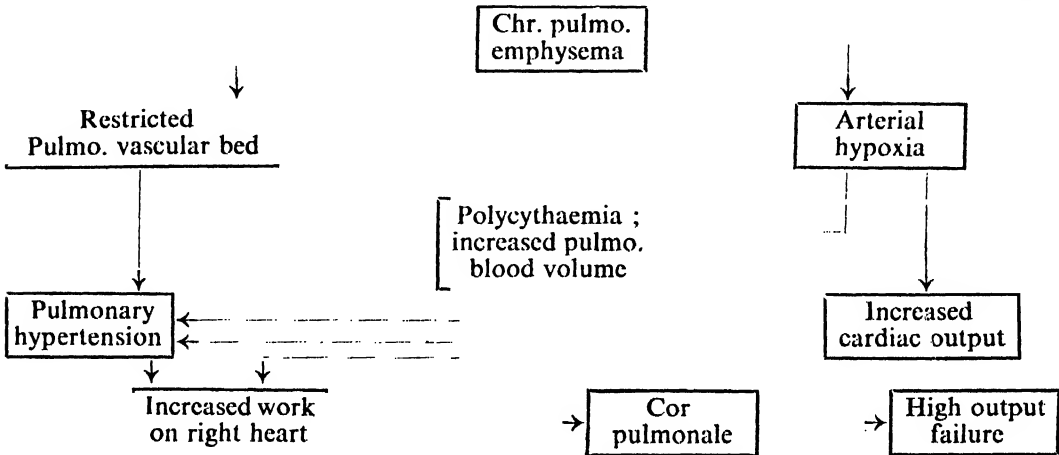
Hypoxia leads to central cyanosis, vasodilatation, increased cardiac output (McMichael and Sharpey Schafer, 1944) and polycythaemia, transient pulmonary vasoconstriction (Motley et al, 1947). This is a heavy burden on the right ventricle. Hence it is common to find that congestive failure is precipitated during acute episodes of infection. Mounsey et al (1952) however, failed to lower pulmonary arterial pressure on administration of oxygen in emphysematous subjects. Carbon dioxide retention has, however, been found to correlate well with

total pulmonary resistance and pulmonary arteriolar resistance (Yu et al, 1953). It has been observed that hypoxia does not act directly upon either the lung or the postarteriolar segment of pulmonary vascular tree to increase pulmonary vascular resistance of blood flow (Fishman et al, 1955).

(2) In obstructive pulmonary emphysema due to bronchial obstruction, there is hyperinflation of alveoli and gradual loss of elasticity, overdistension and rupture of alveoli (Christie, 1952). Capillaries are lengthened, narrowed and compressed by high intra-alveolar pressure. As alveolar septa rupture the capillaries are destroyed. This initiates the development of obliterative pulmonary hypertension.

The combination of hyperkinetic circulation due to hypoxia along with pulmonary vasoconstriction and reduction of pulmonary vascular bed leads to development of pulmonary hypertension. The right ventricle hypertrophies and ultimately fails.

The scheme below indicates the oversimplified mechanism of failure of cor pulmonale :



(After Richards and Fishman, 1956)

**Clinical Features:** The patient is usually an elderly person with a history of chronic cough, mucopurulent expectoration or attacks of bronchial asthma. He may also complain of weakness and fatigue and progressive exertional dyspnoea followed by oedema of the legs which is often seen after an attack of bronchitis or bronchopneumonia. Headache is another complaint which is said to be due to increased C. S. F. pressure resulting from CO<sub>2</sub> retention (Davies et al, 1949), (Flint, 1954). There may be a history suggestive of chronic pulmonary tuberculosis, bronchiectasis or attacks of bronchopneumonia.

Examination shows dyspnoea, cyanosis and frequently clubbing of the fingers and toes.

The chest is emphysematous with diminished respiratory excursion, obliteration of hepatic and cardiac dullness and weak air entry. The neck veins may be distended due to emphysema.

The apical impulse is often impalpable, but heaving impulse in the left parasternal region or xiphisternal junction or epigastrium may be felt due to hypertrophied right ventricle.

Samuel Oram (1956) employs a manoeuvre for feeling the heave of the hypertrophied right ventricle by placing the ring and little fingers over the 3rd and 4th left intercostal spaces respectively, while the index finger over the 2nd left interspace and the middle finger over the 3rd costal cartilage feel the closure of the pulmonary valve and pulsation of the pulmonary artery respectively.

The heart sounds are difficult to hear and the pulmonary second sound may be accentuated and split.

Ophthalmoscopy may show retinal venous engorgement and papilloedema due to CO<sub>2</sub> retention (Simpson, 1948) though papilloedema may be due to concomitant polycythaemia (Meadows, 1947). However none of Simpson's cases had marked polycythaemia.

The onset of failure is manifested by further engorgement of neck veins, enlargement and tenderness of the liver, positive hepato-jugular reflex and peripheral oedema. Protodiastolic

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gallop may be heard at the left sternal border and murmur of functional tricuspid incompetence may be audible. The extremities which are warm in the stage of compensation become cold and blue.

The electrocardiogram shows sharp peaking of the P wave (P pulmonale) which is possibly the earliest sign of right ventricular involvement in emphysema (Wood, 1956) in Leads II, III and aVF. There may be RS-T depression with inversion of the T in leads overlying the right ventricle in addition to right axis deviation and clockwise rotation. There may also be tall R waves in  $V_1$  and  $V_2$ .

X-ray will show increased radiotranslucency, prominent pulmonary artery and hypertrophy of the right ventricle (though difficult to demonstrate). Enlargement of the right auricle is rare in the absence of failure.

**Diagnosis :** It is very difficult to decide whether the heart has been involved in emphysema or not. However, left parasternal or epigastric heave, accentuated pulmonary second sound, electrocardiographic evidence of right ventricular hypertrophy and strain, and X-ray evidence of right ventricular hypertrophy and enlargement of the pulmonary artery will indicate cardiac involvement. In case of failure, peripheral cyanosis and oedema, hepatic enlargement with tenderness, hepato-jugular reflex and protodiastolic gallop in the left parasternal region along with P pulmonale and right ventricular strain in the E. C. G. will make the diagnosis clear.

**Prognosis :** Prognosis is very grave once congestive cardiac failure supervenes. Many cases die within one year, unless the primary cause and the aggravating factors can be relieved to some extent.

**Management :** Energetic treatment should be undertaken to prevent involvement of the heart in cases of chronic bronchitis and emphysema. Once the heart is involved, the emphysema is far advanced.

The management consists of (1) relief of cough with expectoration, (2) relief of bronchospasm and hypoxia, (3) control of bronchopulmonary infection.

As discussed previously infection plays an important role in production of pulmonary hypertension. May (1953) studied organisms associated with chronic bronchitis (commonest association of pulmonary emphysema) and found that pneumococcus and H. influenzae were the two most important organisms. Hence injection of penicillin combined with streptomycin usually produces striking improvement. If these drugs fail, the best alternative treatment suggested is by one of the tetracycline group. Helm et al (1954) have found beneficial results by long term treatment with oxytetracycline in patients of cor pulmonale. Though chloramphenicol is the best drug against H. influenzae, it is avoided as repeated use of this drug may cause development of aplastic anaemia (Daley and Miller, 1956).

Parenteral administration of adrenaline helps in relieving bronchospasm in cases of bronchial asthma. Administration of aminophylline or isopropyl noradrenaline is useful in some cases. Choline theophylline 500 mg t.d.s. by mouth (Wood, 1956) has been suggested as a substitute. ACTH and cortisone are also useful.

Anoxia should be treated by intermittent  $O_2$  inhalations. Continuous  $O_2$  inhalation however may cause narcosis due to retention of excessive  $CO_2$  by removing the anoxia which is the main stimulus to respiration in these cases (Davies and McKinnon, 1949). However, Westlake et al (1955) have shown that insensitivity of the respiratory centre may be due to anoxia itself and may recover when  $O_2$  is supplied.  $CO_2$  retention may be treated by intermittent positive pressure respirator or by Drinker's apparatus.

In cases of failure, with cold blue extremities, small pulse and low B.P., the patient should be treated with bed rest, intermittent  $O_2$  inhalations, low sodium diet, digitalis or strophanthin group of drugs, injection of mersalyl or administration of Diamox. Howarth, McMichael and Sharpey-Schafer (1947) had shown that high output tended to fall if venous pressure was lowered and as these workers considered digitalis to be a primary venous pressure-lowering drug, they advised withholding of digitalis in cor pulmonale. However, the idea of primary venous pressure-lowering action of digitalis has been abandoned (McMichael, 1952). Hence digitalis can safely be given in cor pulmonale. Strophanthin is better than digitalis in many cases. "Strophanthin may be the drug of choice in collapsed cases of cor pulmonale" (Wood, 1956). Diamox is said to have a special place in the treatment of chronic cor pulmonale. It not only lessens oedema by excretion of sodium but also lowers plasma bicarbonate level.

However, larger doses tend to produce metabolic acidosis and inhibition of erythrocyte carbonic anhydrase (Richards and Fishman, 1956). Venesection should better be avoided, though repeated venesection in small amounts is better tolerated and is indicated if there is evidence of increased blood volume (Richards and Fishman, 1956).

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## PULMONARY LEPROSY, RADIOLOGICAL CHANGES IN—See RADIOLOGICAL CHANGES IN PULMONARY LEPROSY

### PULMONARY TUBERCULOSIS, TREATMENT OF

P. K. Ghosh

Concepts regarding various problems of tuberculosis have undergone tremendous changes during recent years. The discovery of streptomycin, PAS and isonicotinic acid hydrazide in quick succession has ushered in an era of new hope in the treatment of tuberculosis. These drugs are effective in tuberculosis treatment, but have their shortcomings too. The search for newer and more powerful drugs however continues. The mortality from tuberculosis in many countries has dramatically fallen, the morbidity rate has also fallen but not so spectacularly. The type of disease also seems to be changing. The death rate from miliary and meningeal tuberculosis has definitely fallen as also the incidence of such cases. The position of rest as the sheet anchor in the treatment of tuberculosis has been seriously assailed. The newer drugs are controlling toxæmia and helping the absorption of exudate and a patient need not be now enjoined long periods of rest. Opinions still differ as to the period of total and minimum rest required by a patient, but there is unanimity of opinion that prolonged rest, as in former times, is no longer necessary. As a corollary to this concept and also as a sequela to the discovery of effective antitubercular drugs, ambulatory treatment and chest clinics are assuming an increasingly important role in the treatment. The demand on hospital beds is decreasing, and in many advanced countries sanatoria beds are lying vacant. The newer antimicrobials and improved techniques in thoracic surgery especially resection surgery, have reduced operative mortality to a minimum and are conferring increasing benefits on chronic invalids. In the field of prophylaxis B.C.G. and vole vaccines have opened up new vistas, and the results of the widespread use of B.C.G. vaccine throughout the world in the post-war period is awaited with expectancy. The use of isoniazid has been advocated in cases of recent tuberculin-converts as a preventive to development of primary and post-primary progressive tuberculosis. Its results are still awaited. In short, a positive and dynamic approach to the intricate problems of tuberculosis with varying success has been the keynote of the last decade.

*Streptomycin and dihydrostreptomycin* are powerful antitubercular drugs. The usual route of administration is intramuscular in a dose of 20mg/kg daily, or intrathecal, 100mg. It is given 1 g daily in acute cases and 1 g, 2 or 3 times a week in subacute or chronic cases. Bacillary resistance to streptomycin develops in 6 weeks on daily administration. It is therefore customary to space out this dose over a longer period. Simultaneous administration of PAS or INH, delays emergence of resistant strains over longer periods. Streptomycin is therefore always given in a combination with PAS or INH. It is more useful in acute rather than chronic conditions and is specially indicated in miliary, meningeal, laryngeal and endobronchial, and acute exudative pulmonary tuberculosis. It is also successfully used in many extra-pulmonary tubercular conditions.

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Streptomycin may produce toxic symptoms like skin eruption, from mere erythematous rash to exfoliative dermatitis, vomiting, giddiness, deafness, bladder dyskinesia, occasionally thrombopenic purpura and aplastic anaemia. It is specially toxic to the eighth cranial nerve. Streptomycin produces comparatively more vestibular disturbance (giddiness), and dihydrostreptomycin more nerve deafness. The earliest changes noticed are usually tinnitus and/or mild loss of appreciation of high tones. Auditory disturbances can occur during therapy or sometime after cessation of therapy—they may progress even when therapy is discontinued.

*Para-aminosalicylic Acid:* The acid is irritant, and is therefore commonly used as a sodium or a calcium salt. Its absorption is hampered if it is given in a resinous coat<sup>15</sup>. Contrary to popular belief the calcium salt does not maintain a longer PAS level in the blood than the sodium salt<sup>15</sup>. But calcium is anti-allergic and is preferred when sodium salt is not tolerated. PAS has less antitubercular activity than either streptomycin or INH. The usual route of administration is oral, 12g daily in divided doses after meals. In severe cases it is also given by continuous intravenous drip in 4 per cent solution. It can also be injected intrapleurally but not intrathecally. Its main action is a synergistic action to streptomycin or INH. It also delays the emergence of resistant strains of tubercle bacilli to either streptomycin or INH. PAS presumably acts by prolonging rather than by augmenting the initial response to streptomycin. The effectiveness of PAS with INH may be partially due to elevation of serum concentration of biologically active INH by PAS in many patients. This action has been explained by competition of PAS with INH for the acetylation capacity of the host<sup>23</sup>. Twelve g PAS daily in three divided doses maintain a concentration of 2 mg of biologically active drug per 100 ml for a longer period than a single large oral dose or rapid intravenous infusion. The simultaneous oral administration of 0.5 g Benemid every 6 hours in patients receiving PAS increases the plasma concentration of PAS by approximately 30 per cent. Benemid has no anti-tubercular property, but it is valuable as a means of increasing the plasma concentration of PAS in patients who can tolerate only small doses.

PAS is bulky to administer, expensive and toxic. The reported toxic manifestations of PAS are many. The commonest is gastro-intestinal irritation—anoxia, nausea, vomiting, diarrhoea and toxic hepatitis. It may produce albuminuria, drug eruption and drug fever. It may attack the haemopoietic system and produce lymphadenopathy and leukaemoid reaction. Hypopotassemia and prolongation of prothrombin time have also been reported. In a few cases it produces goitrous and hypothyroid states, especially in women, but these quickly disappear on withdrawal of the drug. The action is believed to be due to PAS blocking intake of iodine by thyroid—iodine does not help in these cases, but thyroid extract is of help<sup>4</sup>. PAS in diet neutralises vitamin C, which is necessary for synthesis of di-iodo-tyrosine and consequently of thyroxine. It has produced near fatal shock followed by neuro-myelo-radiculoneuritis of Guillain-Barre<sup>7</sup>. Many of the toxic symptoms can be reduced by simultaneous administration of antacids e.g. sodium bicarbonate, aluminium hydroxide, etc. But they also interfere with the absorption of the drug and there is consequently lower serum concentration. PAS conjugated with vitamin C is tolerated well and maintains a sustained drug concentration in the blood.

*Isonicotinic Acid Hydrazide:* It is the most potent drug in the treatment of tuberculosis. It is cheap, has very low dose and very low toxicity, and is therefore a safe drug. It is easily and totally absorbed from the alimentary canal, and is excreted in the urine. It diffuses readily through body fluids and tissues, and is even found among caseous glands. It is excreted into the cerebrospinal fluid. Its use has therefore made intrathecal medication unnecessary in the treatment of meningeal tuberculosis. It is used in doses of 3 to 5 mg/kg per day in average cases or in 200-300 mg daily doses. It can be given in much higher doses. Children tolerate INH much better than adults. Paediatricians have obtained striking therapeutic results in miliary and meningeal tuberculosis by means of simple administration of INH, in very large daily doses of 20-30 and even 40 mg/kg of body weight<sup>29</sup>.

One significant disadvantage with this drug is the early emergence of resistant strains of tubercle bacilli to it—some strains are also naturally resistant. In one trial<sup>26</sup> with 156 patients with INH alone, half the strains of tubercle bacilli had become resistant to the drug in three months. But with PAS and INH in combination this resistance did not develop in a three months period. It has been suggested that PAS may block the partial inactivation of INH by acetylation. The drug is therefore preferably used in combination with streptomycin, PAS or some other suitable drug. As both streptomycin and isoniazid are potent drugs, PAS in com-



bination with either is recommended in an average case, so that streptomycin or INH is left over for any emergency at a later date.

INH has also been used alone in the treatment of tuberculosis for periods varying from six to fifteen months in chronic cases. The different studies prove that INH alone has a definite therapeutic value in such cases. In one study<sup>10</sup> 47 patients with moderately or far advanced disease were started on INH alone—32 continued INH for full one year. At sometime during the year, 29 of the 47 patients were classified as having substantial radiological improvement and 6 were worse radiologically. 44 patients had cavitary disease—cavitary closure occurred in 15 without collapse or resection therapy. At the end of the year, tubercle bacilli could be cultured from approximately one-fourth of the original 47 patients.

*Do INH-resistant strains produce disease?* The emergence of resistant strains of tubercle bacilli to INH has received great attention. This resistance is related to the catalase activity of the bacilli. INH-resistant catalase-positive strains may contain virulent forms. But INH-resistant catalase-negative strains failed to multiply in a number of host animals and failed to produce disease in certain susceptible animals e.g. guinea-pigs, but not in others e.g. the mouse. It was fondly hoped that in man the INH-resistant strain might not produce progressive disease, but this hope has not yet been substantiated. However, in clinical practice many patients discharging INH-resistant tubercle bacilli show general clinical improvement and new lesions rarely develop in other parts of the respiratory tract or body. It may be assumed that INH resistance may not have the same alarming significance as resistance to streptomycin or PAS<sup>11</sup>.

*Toxicity:* Though INH is the least toxic of the known antitubercular drugs, yet in susceptible persons and with overdosage toxic manifestations have been described. The chief two manifestations are hepatotoxic and neurotoxic. In doses of over 8 mg/kg daily peripheral neuritis, hyperflexia, convulsions, psychosis and neuropathies have been reported. But these are reversible and disappear on withdrawal of the drug. *Its use in known epileptics is contra-indicated.* The peripheral neuritis has been ascribed to its interference with pyridoxine metabolism, and is preventable by simultaneous administration of 25 mg/kg pyridoxine per 8 mg/kg INH per day. Neuritis identical to INH neuritis may be seen in human pyridoxine deficiency induced by desoxypyridoxine, a metabolic antagonist of pyridoxine<sup>3</sup>. Other minor manifestations are interference with carbohydrate metabolism (hyperglycaemia), production of pellagra, constipation, suppression of urine, etc. Therefore, *its use in cases of diabetes mellitus* should be carefully watched and regulated. Isoniazid bears a close structural similarity to nicotinamide and can replace it in DPNL (diphospho-pyridine-nucleotide) and thus precipitate pellagra in pre-pellagrous patients<sup>18</sup>. In some cases INH produces drug fever; it is therefore desirable to begin with small doses of INH and then to give the appropriate higher dose. In *lupus vulgaris* vit. D<sub>2</sub> was till now the drug of choice. Russell and Thorne<sup>25</sup> have reported very good results with INH in lupus using 300 mg dose per day for a period extending upto at least 3 months after clinical clearance.

*Streptomycin, PAS and INH:* Due to the early emergence of bacillary resistance against single drugs, combination of drugs has been employed in the treatment of tuberculosis. The British Medical Council<sup>5</sup> in its seventh report recorded the results of clinical trials of various combinations of streptomycin, PAS and isoniazid in 588 patients over a period of three months.

The drugs were used in the following four combinations—streptomycin 1g and isoniazid 200 mg daily, streptomycin 1g twice weekly and INH 200 mg daily, sodium PAS 20 g and INH 200 mg daily, and sodium PAS 10 g and INH 200 mg daily. According to this report streptomycin 1 g daily and INH 200 mg daily produced the best results.

The Veterans' Administration Study<sup>27</sup> in its report in 1955 recorded the results of similar combinations in a much larger group of patients. The dose of INH was higher—300 mg daily against 200 mg daily in the British report. Three hundred mg INH and 12 g PAS daily, 300 mg INH daily and streptomycin 1 g twice weekly and 12 g PAS daily and streptomycin 1 g twice weekly, were used in 2187 pulmonary tuberculosis patients over a period of three months. The patients were divided into three groups and the extent of the disease in each group was comparable. Treatment with INH and PAS daily gave significantly better results in advanced cases and those with large cavities; INH and PAS combination was also more effective in reversing infectiousness. In the case of minimal pulmonary tuberculosis the results of the three



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treatment regimens were almost equal. The result also seemed to show that INH was superior to streptomycin or PAS, and any chemotherapy in tuberculosis should therefore include INH.

**ACTH and Corticosteroids :** The corticosteroids in experimental animals and in human beings have been known to aggravate the disease. Pulmonary lesions have occurred in persons not known to be previously suffering from tuberculosis. They have therefore been avoided in the treatment of tuberculosis generally. The therapeutic effects of the steroids are anti-inflammatory, antiallergic and antitoxic, and are definitely not due to inhibition of the growth of the offending organisms. In moribund cases and in miliary and meningeal tuberculosis these steroids have therefore been used to whip up the defence mechanism of the body, and several successful reports have been published. A large series of 160 cases has been reported by French doctors<sup>13</sup> who used ACTH and cortisone (50 mg daily for 3 weeks) in association with streptomycin and INH. They claim that by a combination of hormone and antibiotic therapy in pulmonary tuberculosis, infiltrates and recent nodules may clear up in 3 weeks. Cavities also close—in their series of 36 cavities, 14 were cured and 9 improved. In chronic cases hormone therapy is less helpful. Even in such cases hormone therapy is beneficial to those who are intolerant to antibiotics, to improve the general condition in severe cases, and to aid in preparation of the patient for surgery. The African natives are known to be easy victims of tuberculosis. Handley<sup>16</sup> published a preliminary report on 23 Bantu females from 12 to 45 years of age, treated for 3 months with 15 mg prednisone and 15 mg/kg isoniazid daily. They were suffering from advanced, bilateral, progressive, cavitary pulmonary tuberculosis—had at least 6 months' previous hospital treatment and had been deteriorating; the prognosis varied from poor to extremely bad. No patient died during the period of observation, although a fatal outcome would have been anticipated in the majority of such cases. All patients showed marked clinical improvement and all gained in weight except one. The sputum remained positive in all patients, and slight Roentgenologic improvement was noticed in only five—there was no deterioration in others. In *post-primary tuberculosis*<sup>9</sup> combined treatment has achieved best results in acute disease. There is also evidence that cortisone is of value in relieving the bronchial stenosis of primary disease.

The bogey of ACTH and related steroids aggravating or activating tuberculous process is today foundering. Used alone they may be dangerous, but used in combination with effective antitubercular drugs they enhance the action of the latter. The future holds promise for a wider use of such combined therapy in acute, moribund and refractory cases.

The corticosteroids have also been used in tuberculosis to treat or prevent allergic reactions of patients to streptomycin or PAS. They are also known to depress tuberculin sensitivity of patients. If 30 mg or more of ACTH is administered daily, the tuberculin test with the first strength of P.P.D. is negative.

**Other Drugs :** The tubercle bacilli get resistant to a drug sooner or later, and the efficacy of the latter suffers. The search for newer and more potent drugs continues in the laboratories of the world. Some of them are reviewed below.

Among the antibiotics may be mentioned *neomycin*, *viomycin*, *cycloserine*, and *terramycin*. The two former drugs have proved antitubercular value, but they are toxic to men—hepato- and nephro-toxic. In clinical trials the results have not justified their wider use. I have personal experience of viomycin in several advanced cases where the three common anti-tubercular drugs had been used previously—it failed to bring about reduction of temperature, sputum conversion and clinical improvement.

*Cycloserine*<sup>11</sup> is not effective in animal tuberculosis, but is effective *in vitro* tuberculosis. It is claimed to be a safe and effective anti-tubercular drug for man, and to produce results comparable to those produced by other anti-tubercular drugs in previously untreated cases. It also provides an effective anti-microbial agent in patients who have failed to respond to other drugs, particularly where surgery is contra-indicated. Its dose is 20-25mg/kg per day, or, 1.0 to 1.5 g per day in adults when used alone and continued as long as 14 months. The major toxic effect of cycloserine was the occurrence of convulsions. If INH is combined with cycloserine, the therapeutic effect was enhanced. *Terramycin* has also been used in the treatment of tuberculosis. But it has been used more for preventing development of resistance to streptomycin or INH than for its antitubercular activity.

Among other chemotherapeutics used in tuberculosis may be mentioned *thiosemicarbazones*, *pyrazinamide*, *iproniazid*, and *hinconstarch*. *Thiosemicarbazones* are oldest in this list, and were extensively used by Domagk in Germany where streptomycin was not easily available in the post-war period. He claimed good results. There are 4 different preparations named respectively TB<sub>1</sub>, TB<sub>2</sub>, TB<sub>3</sub> and TB<sub>4</sub>. They are all toxic—toxic to the kidney, the liver and particularly to the haemopoietic system. Except TB<sub>1</sub>, the others are not in use to-day. The dose of TB<sub>1</sub> is 100-150 mg per day; repeated blood counts and urinalysis are necessary. *Pyrazinamide* (aldinamide) is used in doses 20-30 mg/kg per day either alone or with INH, streptomycin or PAS. A few authors have reported good results. The drug is powerfully hepatotoxic, and should be used with great caution. Various other preparations derived from INH or from combinations of INH and other drugs such as *hinconstarch*, *isorilone*, *iproniazid*, etc. are being tried out, but have not found their place in the routine treatment of tuberculosis.

**Drugs and Collapse Therapy:** Several workers have doubted the value of simultaneous administration of antimicrobials during the course of artificial pneumothorax and pneumoperitoneum treatment. They seem to think that drugs do not reach the collapsed lung in sufficient concentration to be effective. In practice antimicrobials are widely used along with collapse therapy and clinical results seem to justify their combined use as and when necessary.

**Vitamins and Antimicrobials:** During treatment with antimicrobials vitamins should be administered. This is particularly true for the vitamin B complex factors which are synthesised naturally in the gut by the activity of the intestinal flora. When antimicrobials are administered the bacterial flora in the intestines is modified and vitamin B deficiency is particularly noticeable. It is therefore necessary to administer vitamins during antimicrobial therapy.

**Primary Pulmonary Tuberculosis:** Antimicrobial therapy has been used in primary tuberculosis with good results. The mortality among children admitted to Bellevue Hospital<sup>22</sup>, New York, with primary pulmonary tuberculosis was 21.5% for 1930-46, 5% after treatment with streptomycin and PAS, and only 1.5% after introduction of INH. Combination of PAS and INH has consistently given good results in some reports. INH alone is also reported to yield good results. There is also evidence that INH may prevent the development of complications of primary tuberculosis, especially miliary and meningeal tuberculosis. In general, in acute cases streptomycin and INH together, and in other cases PAS and INH together seem to be the treatment per choice.

**Cavitary Closure:** With chemotherapy alone closure of lung cavities in tuberculosis may be expected in a considerable number of cases. Ross and Kay<sup>21</sup> reported closure of tuberculous cavities under chemotherapy in 138 cases—92 had only chemotherapy, 46 had surgery also; 6 relapses were reported. Cavity closure has long received great attention from phthisiologists, and increasing emphasis has been laid in recent years on closure or resection of the cavity. The combination of drugs now available may close some cavities, sterilize others and suppress bacterial multiplication, and thus shift the present emphasis on surgical procedures.

**Miliary and Meningeal Tuberculosis:** Streptomycin and INH are to be used together and in high doses. Streptomycin is given 1 g twice daily for some days and then in 1 g daily doses. INH is also given in 8-10 mg/kg or even higher daily doses. In meningeal tuberculosis streptomycin is given intramuscularly and intrathecally, in doses of 100 mg. INH can be given orally, parenterally and intrathecally. But as INH is excreted in the cerebrospinal fluid in sufficiently bacteriostatic concentration, intrathecal administration of streptomycin or INH are not generally advocated to-day. The treatment should be continued till the cell count in cerebrospinal fluid returns to near-normal. Afterwards, streptomycin is withdrawn, and PAS and INH continued for one to two year period. Formerly death from meningeal tuberculosis was near cent per cent. To-day the recovery rate has come upto 50 per cent and more—and even upto 100 per cent in a Spanish report. Some sequelae may remain behind—a cranial nerve palsy, mono- or hemiplegia, or mental dulness. In earlier days when streptomycin was used alone or with PAS, nerve deafness, blindness and hydrocephalus were comparatively common. It was debated whether hydrocephalus resulted from streptomycin, or followed adhesions and fibrosis which are normal reparative processes in tuberculosis. The majority opinion exonerated streptomycin and attributed hydrocephalus to reparative processes, consequent on longer life in streptomycin-treated cases. With introduction of INH even these sequelae are getting less. INH cannot relieve hydrocephalus once it is formed after streptomycin, but given early, INH may prevent it. The prognosis of miliary tuberculosis has similarly changed for

## Pulmonary Tuberculosis, Treatment of

the better, and deaths are rare. In a case under the writer's care, in the pre-INH days, the miliary mottlings, after 30 days of 1 g streptomycin daily became less pronounced and still more so after 60 days; they completely disappeared after 75 g streptomycin. The patient is still alive and healthy even after 9 years. In miliary tuberculosis INH and streptomycin are used together and also in high doses. They can be also used alone. Early relapse after INH alone in miliary tuberculosis is not common, if at all it occurs. Relapse of miliary tuberculosis in contrast, is frequent under streptomycin when this is given alone.

*Surgery of Pulmonary Tuberculosis:* In spite of sufficient rest and chemotherapy, certain localised lesions in the lung resist healing, remain potentially active and may initiate bronchogenic spread. The surgeon has to deal with such localised lesions of a generalised disease, and has the choice of collapse or resection therapy. For a long time collapse therapy held sway—A.P., P.P., phrenic operation, plombage and thoracoplasty. Recent study of broncho-pulmonary segments and improved surgical techniques have brought resection to the forefront of surgical treatment. Plombage and thoracoplasty are choices for upper lobe cavitory or caseous disease—plombage is more suitable for cases where there is a complicating non-tuberculous disease, gross impairment of ventilatory function, or far advanced cavitory tuberculosis. Many surgeons will object to plombage for they do not prefer to leave a space-occupying foreign material inside the body. They will rather prefer to do a thoracoplasty. A very large proportion of cavities occurs in the apex of the lung, and so "mobilisation of the apex" forms the basis of all modern thoracoplastic procedures. Resection<sup>20</sup> is indicated for tuberculomas, dorsal lobe cavities, bronchostenosis and bronchiectasis, "destroyed lung", thoracoplasty failures and any caseous nodule<sup>2</sup> of over 2.5 cm in diameter. Resection is also indicated for cavities situated in the middle lobe, lingula and basal segments of the lower lobe. Resection includes pneumonectomy, lobectomy and segmental excision. After the first two operations there is a tendency for the remaining lung to overdistend and fill up the residual space resulting in reactivation of disease. A corrective thoracoplasty<sup>2</sup> excepting in minor segmental excisions is therefore obligatory either at the time of excisional surgery, or two to three weeks later. Resection has also been advocated in certain types of primary tuberculosis<sup>17</sup> in childhood, viz. compression of trachea causing respiratory distress and a glandular mass visible on radiography causing distortion of a bronchus or bronchial obstruction and pulmonary collapse. Resection does not cause deformity like thoracoplasty, removes the offending focus of continued activity permanently and is a safe procedure to-day (the overall mortality is 2 per cent or even less).

*Ambulatory Treatment:* The 14th International Conference<sup>8</sup> on Tuberculosis held at Delhi, early last year, discussed this form of treatment extensively at one of its sessions. German, Russian and other scientists discussed on a nation-wide basis, and their reports unanimously established that ambulatory treatment of pulmonary tuberculosis is an effective method of treatment in both advanced and underdeveloped countries, even for advanced and cavitory cases. The Russian report was based on a study of 9442 patients and the German report on 9648 patients. Of the latter 5988 were cases of active pulmonary tuberculosis (infectious and non-infectious) treated with ambulatory chemotherapy alone—of them 75 per cent were cured or improved, 25 per cent remained unchanged or deteriorated. Of the 2855 cases of open (infectious) pulmonary tuberculosis treated only with ambulatory chemotherapy 66.4 per cent became non-infectious. The Russian report on sputum conversion was 46.42 per cent in 1112 positive patients—the conversion was more rapid and of a more permanent nature in moderately advanced cases (76.5 per cent) and less marked in far advanced cases (24.7 per cent). The latter also reported that chemotherapy had considerably less effect on closure of cavities under ambulatory conditions, serial X-rays showing a closure of cavities in 22.5 per cent of cases.

Middlebrook, Dressler and others<sup>11</sup> reported in 1954 that in controlling the acutely active disease and its clinical toxicity, INH alone or with other drugs was more dramatically and consistently effective than rest in any form and that treatment in a hospital without long term bed rest had no deleterious effect on the tuberculous infection. They further stated that tubercle bacilli still viable but metabolically dormant in closed necrotic lesions might open up and cause reactivation after movement and should be given every opportunity to open up under protection of chemotherapy with INH. Use of INH alone or with other drugs to decrease the incidence of tuberculous relapse would thus require intentional abandonment of long term physical rest,

**B. C. G. Vaccine and Vole Vaccine :** Can tuberculosis be prevented by vaccine ? The question has been hotly debated ever since Bacille Calmette-Guérin vaccine (B.C.G.) was first used in man. After the Lübeck disaster in Germany in 1930, where 73 out of 249 children died of tuberculosis, B.C.G. fell into great disrepute. Though it was proved at the trial that B.C.G. vaccine was in no way to be blamed, and that the deaths were due to using a vaccine made from a virulent human strain by mistake, people were afraid to try B.C.G. vaccine. However, the Scandinavians revived its use in the period following the Second World War. Strong scientific evidence in favour of its efficacy was collected. Heimbeck's<sup>19</sup> work among nurses in Oslo, Aronson and Palmer's<sup>1</sup> work among American Indians, and British Medical Research Council's Report<sup>6</sup> on B.C.G. and Vole vaccines (1955) gave strong support to the efficacy of B.C.G. vaccine against tuberculosis. But the immunity conferred by B.C.G. vaccine is less potent and of shorter duration. In about three to four years the immunity of B.C.G. vaccine fades away, and the individual has to be re-vaccinated. This is an important point to bear in mind. Cases are reported from time to time where tuberculosis has developed among vaccinated persons. But their number is small, and in all cases which have been bacteriologically examined the lesion has been traced to human bacillus. The Vole vaccine has been claimed to confer stronger and longer immunity, and in this respect to be superior to B.C.G. vaccine<sup>28</sup>. But its very recent origin and its very limited use preclude its assessment yet.

The next question is : *How safe is B.C.G. vaccine ?* In the Indian subcontinent itself about 30 million people and a similar number of persons in other countries have been vaccinated. Only two authenticated cases of death have so far been reported. One was a seven year old Danish boy who became unwell two weeks after vaccination and died two years after. On culture pure B.C.G. was grown from various organs; this is the only recorded case of B.C.G. producing a progressive generalised infection in a human being. The second death was in a French infant who was vaccinated a few days after birth and in whom there was severe glandular swelling and large amount of pus discharged at tenth week. The infant died of fever and toxæmia after 3 months. Animal inoculation of the pus showed no progressive tuberculosis. Except these two cases no progressive disease with B.C.G. has been reported. Complications of B.C.G. vaccine are rare. A few cases of chronic ulcers and keloid formation locally have been observed by the writer and also reported by others. Regional gland involvement with softening and breaking down has also been reported, and has been more common among the neonatal group in our experience. Of our approximate 4000 neonatal cases about 40 had glandular enlargement or softening—roughly one per cent of cases. The majority healed spontaneously or after aspiration in a few cases; streptomycin was also used in a few cases. Due to this complication, vaccination of the neonate has been abandoned in West Bengal. A few cases of hilar enlargement on radiographs of lungs between the sixth and thirteenth weeks, and a few cases of erythema nodosum at the time of conversion have been reported<sup>24</sup>. On the whole B.C.G. vaccine can be considered as safe.

**Chemoprophylaxis<sup>12</sup>:** INH is a safe drug, and children tolerate it much better than adults. A dose three times larger than that which is commonly used in treatment will not cause any harm to the children, and is easily taken as tablets or chocolates. It has been used in veterinary practice as a prophylaxis against tuberculosis. Children and adolescents with signs of primary infection should be treated with antimicrobial drugs. But what about children who have been converted recently but are without radiographic or other evidence of disease ? At a conference held at Centre internationale de l'enfance in Paris in 1955, many workers agreed in advising antibacterial treatment for all converters at least up to the age of 2-3 years. Recently Zorini<sup>29</sup> strongly advocated its use in a well-documented paper. In some countries tuberculin negatives are B.C.G. vaccinated and tuberculin positives are given INH. In some other countries INH is being advocated to be given to all children who are exposed to infection, irrespective of whether they are tuberculin positive or tuberculin negative. INH is being increasingly used for chemoprophylaxis.

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## RADIOGRAPHY OF THE CHEST, SECTIONAL

S. S. Katdare

**Synonyms :** Tomography, laminagraphy, planigraphy, stratigraphy, differential radiography.

Since the discovery of conventional radiographic methods, in the early twentieth century by Roentgen and others, attempts were being made by Bocage in 1917, Vallebona in 1930, Zeidses des Plantes in 1933, Grossman in 1935, Kieffer in 1937 and many others to analyse the summation shadows shown on X-ray films of chest. The chest is a composite structure containing anatomically different organs, with different X-ray densities, superimposed on one another. The X-ray picture is again a composite summation of the many shadows of different organs that come across the X-ray beam, projected in one plane only. These shadows have to be differentiated into its components to derive the required information. Sectional radiography or tomography aims at obscuring the unwanted shadows above and below, by a process of movement and diffusion, so that the required layer only is produced on the X-ray plate in maximum detail and with maximum sharpness.

**Historical:** Zeidses des Plantes, a Dutchman and Bocage, a Frenchman, in about 1917-1921 published information on the subject and demonstrated actually in practice that by moving the X-ray tube and the film in opposite directions blurring of the structures above and below the required layer in focus, could be obtained. In doing so all points planoparallel to the film and located within the plane of rotation, will appear on the same points on the film ; on the other hand, all points from other planes of the object, located above and below the plane of rotation, project their shadows on different parts of the film and appear blurred. The end result is the production of one particular plane in maximum detail and sharpness, where no movement takes place at all. Whilst, moving the tube and the film it is essential that the movements must be synchronous and in the opposite directions. A certain relation of the object focus and the object film must be constantly maintained during the movement.

Vallebona and Bozetti in 1930, advocated a method in which the X-ray tube and the film remain stationary and the object moved through an angle, the movement being synchronous and synonymous. Though the blurring of the peripheral points in the object were achieved by this method, the sharpness and details of the object layers were definitely inferior to the method evolved by Bocage, and this was soon given up. In 1935, Grossman and Kremer published papers in which they proved that unilateral blurring obtained by synchronous circular movement of the tube and the film was definitely more informative in producing the focal layer with maximum clarity. In their method they obtained better and more informative tomograms, because of (1) clarity of the focal layer and (2) additional blurring of the out-of-focus layers ; these being made easily possible by the circular synchronous movements.

In 1944, Vieten discussed geometrical problems concerning the tomographic methods, and showed that transverse body section tomographs could be obtained, and a three dimensional

PLATE IX  
SECTIONAL RADIOGRAPHY OF THE CHEST



FIG. 1  
Mr. G. (22)

*A-P tomogram showing a tuberculous cavity situated in the lower lobe of the left lung hidden by the cardiac shadow.*

FIG. 2  
Mr. G. (22)

*Left lateral tomogram showing the cavity at the apex of the left lung of the lower lobe. Lobectomy was done.*



FIG. 3  
Mr. H. (29)

*A-P tomogram showing distinct cavity in the upper lobe of the left lung. The cavity was not seen in scout films.*

FIG. 4  
Mr. N. (38)

*A-P tomogram showing a large cavity situated in the upper lobe of the left lung and embedded in fibrotic tubercular lesion. Tomogram shows spread to the right lung upper lobe. This was not seen in scout films.*

PLATE X  
SECTIONAL RADIOGRAPHY OF THE CHEST

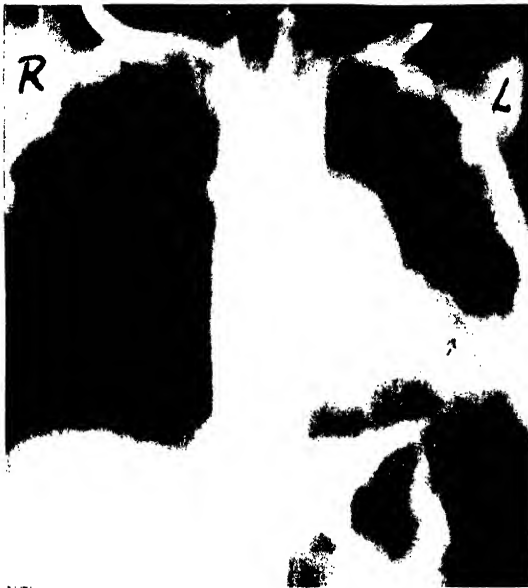


FIG. 5  
Miss C. (22)

*A-P tomogram. Extensive fibrocaseous lesion in the left lung showing a number of cavities in atelectatic segments of the lower lobe.*

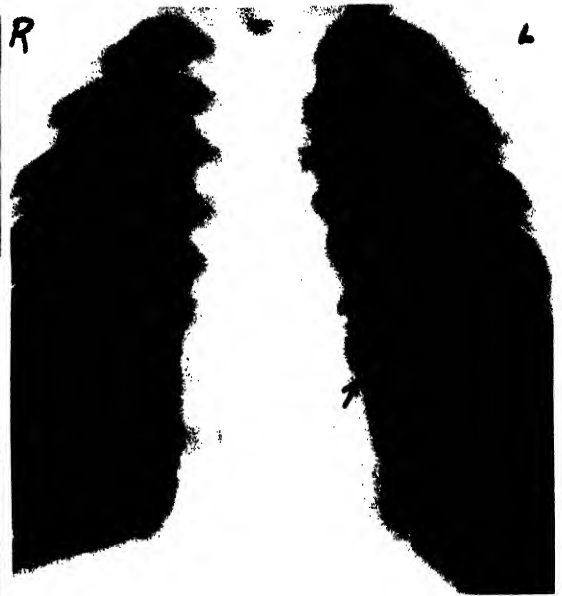


FIG. 6

*I-P tomogram showing a cavity near the pericardiac region in the left lung, partly covered by the cardiac shadow.*



FIG. 7  
Miss X

*A-P tomogram showing residual tuberculous lesion at the left apex. This lesion was not noticed at all in scout films.*



FIG. 8  
Mr. P.

*A-P tomogram. Thoracoplasty done one year ago on the right side. Persistent recurrent cough with sputum. Tomogram showing distinct cavity in the upper lobe of the right lung overshadowed by resected ribs.*

*PLATE XI*  
SECTIONAL RADIOGRAPHY OF THE CHEST



FIG. 9  
Mrs. Q.

*Right lateral tomogram, 7 cm cut showing atelectatic bronchus segment of the lower lobe of the right lung.*

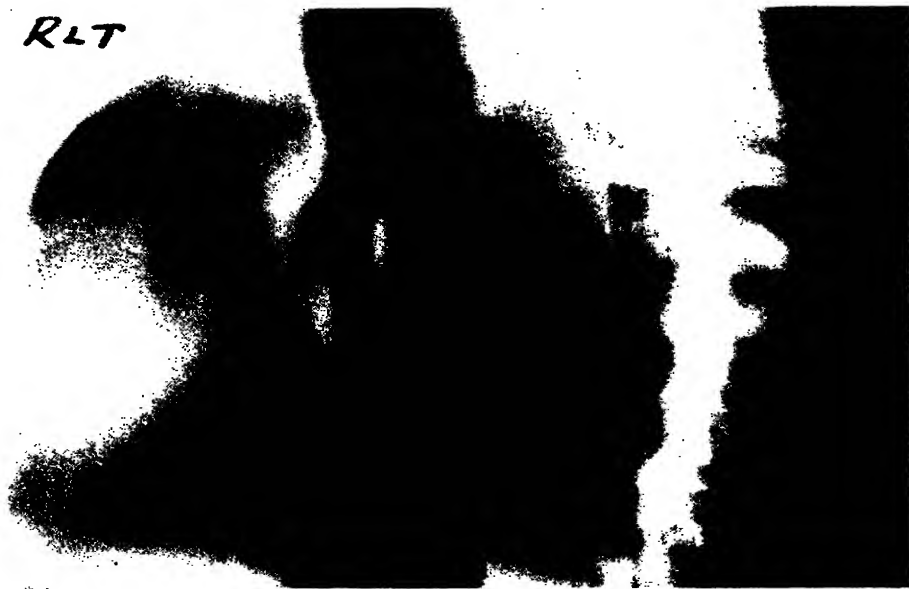


FIG. 10  
Mrs. Q.

*Right lateral tomogram showing bronchiectatic atelectatic lower lobe segment of the right lung, enclosing a number of cavities in 8 cm cut. Complained of cough with expectoration.*



PLATE XII

SECTIONAL RADIOGRAPHY OF THE CHEST



FIG. 11  
Mr. D. (45)

*A-P tomogram 13 cm cut shows a rounded shadow with definite borders situated just underneath the anterior end of 5th rib. Benign tumour, a fibroma.*



FIG. 12  
Mr. X (48)

*Right lateral tomogram 11 cm cut showing a mass of glands at the rt. hilum. Carcinoma of the right lung.*



FIG. 13  
Mr. W. (48)

*Right lateral tomogram. Massive consolidated segment of the right lung, upper lobe, 8 cm cut. Carcinoma of the right lung.*

picture could be produced with unilateral movement of the tube and the film. During 1946-50 Vallebona, Wachsmann, Takahashi and Shinozaki worked on this method of transverse tomography and published their results independently. The underlying principle of their experiments was that the object and the horizontally placed film were moved synchronously through 360 degrees. The principal ray of the fixed tube fell on the object and the film at an angle of 20-30 degrees. The required section of the body at a particular level appeared clearly on the film, whilst the part above and below caused circular blurring. Transverse body section tomographs often yield valuable complementary information to tomograms taken in conventional longitudinal planes. It gives a sort of three-dimensional appearance of the human body.

Attempts were made by Janker, Lysholm, de Abreu and others in 1950 to do screening of a particular layer of the body, to avoid the considerable expense of films taken in routine tomography. The development of Odelca reflex cameras and high-powered optics has made this possible to a certain extent. But this screen-section fluoroscopy photofluorography has its limitation and sufficient information is lacking at the end of the procedure. Siemens recently have manufactured a radioscope with the aid of which one can see the particular layer on the screen, while the tomographs are being taken.

Vietsen (1940) and de Abreu (1947) have suggested methods by which a number of body section tomograms could be taken with a single exposure. The electro-medical industry has for this purpose brought out a specially constructed cassette in which a number of films, and sufficient amount of foil combination is so maintained that several sections are obtained during one exposure. This method if proved satisfactory in the future, may lessen the patient's exposure and thereby radiation hazards of tomography, if any.

Short, Rossi and others (1951) have indicated the possibility of using stereoscopic body section radiography. Vallebona (1936), Kieffer (1938) and Becker (1955) have made use of kymography with section radiography in many of their patients. However, such combinations are encountered with lots of technical difficulties and are also of doubtful diagnostic values.

**Definition :** Tomography can be described as a specialised radiographic procedure, with the aid of which, clear-cut X-ray photographs of a particular layer of the body could be obtained, the layers and structures above and below the particular required layer being blurred and thus obliterated from view. Andrews (1936) defines it as a "method of Roentgenographic projections of plane sections of solid objects. This may be effected by moving the point of source of Roentgen rays in one direction, while the recording medium is covered in opposite direction, the two being moved simultaneously and in constant ratio by means of a connecting system rotating about an axis which lies in the plane of the section to be projected."

**Principle :** The underlying principle is one of diffusion and obscuration of unwanted shadows above and below the 'required layer' (also called the 'layer in focus'), by a process of movement so that the 'required layer' is produced on the film with maximum clarity and definition, all other shadows besides the required layer being blurred. This is achieved by moving the X-ray tube and the Potter-Bucky diaphragm carrying the X-ray film in opposite directions during exposure. The movement has to be synchronous and at a proportionate rate. The film and the tube rotate about an axis in the plane which is required to be radiographed.

**Technique:** The proper technique is a very important factor in procuring tomograms of good quality. For tomography of the chest, about 65-70 K. V. with 40-48 in. distance and 20-30 MAS, usually become sufficient. Linear shadows do appear on the plate, if movement is not even and synchronous. It is very deceptive and useless to take a number of sections without proper planning. Every case is a problem by itself. I usually take three sections, half way between the anterior and posterior planes and then decide as to how to proceed further after viewing these preliminary sections. This becomes a more definite process in hitting the proper plane and, obtaining the requisite information. Usually one cm tomogram, about 7 or 8 sections, are sufficient. Very rarely one is required to take 0.5 cm cuts. Every case should be systematically reviewed and planned cuts taken. The tomograms must reveal beyond doubt what is desired and must elicit definite and useful information. Scores of plates improperly taken at random are worse than useless. Tomographic procedure must never be left entirely to the technician.

**Discussion :** Numerous obstacles are put forward by the inexperienced against the valuable procedure of tomography. The first and the foremost is the plea that many sections are required

## Radiography of the Chest, Sectional

to be taken and the expenses incurred are heavy. One must clearly understand that this is a specialised procedure to procure additional useful information, which conventional methods of X-rays fail to reveal. We are often requested to take the minimum number of plates—a procedure which defeats its usefulness. In this connection, it has been suggested by some workers to use 'spot films' or smaller size plates to obtain the various cuts. It will be interesting to review how often in practice, the tomograms reveal unsuspected lesions of grave significance on the opposite side. One is fully justified in minimizing all the risks and to take a sufficient number of full size plates, to get the best possible advantage. The second objection raised is the likelihood of 'radiation hazard' in exposing the patient to tomographic procedures. Actually the risk is negligible, and is no more than in fluoroscopy of the chest, which is an everyday radiological procedure.

Tomography has played a very important role in advancement of thoracic surgery during the last two decades. During and after the Second World War thoracic surgery made tremendous progress due to the proper understanding of intrathoracic anatomy, physiology and pathological anatomy, so clearly revealed with the aid of tomography. To the thoracic surgeon of the present generation, tomography is a *sine qua non*, without which it is difficult to undertake surgery. Preoperative tomography of the chest may give lot of useful information to the surgeon, and he can be forewarned and forearmed in his subsequent operative techniques. He has to decide beforehand, whether he is going to carry out segmental resection, lobectomy, pneumonectomy, or not carrying out any operative intervention. The responsibility of providing the preliminary information falls to the radiologist in order to help the surgeon in making his surgery simpler.

The most useful application of tomography is in the field of pulmonary diseases firstly in pulmonary tuberculosis, and secondly in detecting early, neoplasms in the chest. Tomography has now been employed for almost all parts of the body. The neurosurgeon and the neurophysician cannot do without tomograms of the vertebral column, where many disc lesions and congenital abnormalities can be clearly seen beyond doubt on the sections. Tomograms of the larynx in early growths are too obvious and self-explanatory. In case of the sternum which overlaps the vertebral column, an AP view of the sternum is impossible, but one clearly sees the whole sternum defined, in the anterior cuts of chest tomograms. The sternoclavicular joints, the temporomandibular joints and cervico-dorsal spine, are yet other examples where conventional radiography fails to give the requisite satisfactory information and in which a tomogram easily elicits the required information.

Majority of the tubercular lesions in the lungs show well on straight X-rays of the chest. But the minimal tubercular lesions are often invisible or masked on straight skiagrams of the chest, taken with modern technique. No chest Roentgenogram should be acceptable which is not taken at 6 ft. distance and has an exposure of more than 0.1. second. Sometimes one finds positive sputum and negative X-ray, though this is rare. It is usually an accidental finding in medical students, nurses and laboratory workers, who are sometimes over-inquisitive about their sputum. On the contrary, it is extremely common to find a definite lesion on X-ray while the sputum repeatedly shows negative results. In almost all these cases where a minimal lesion is suspected, tomography invariably gives positive results showing the nature of the lesion beyond doubt.

In tuberculous lesions which are clearly visible on routine films, the physician or surgeon treating the cases usually seeks more information. The presence or absence of a cavity and the nature of the cavity, do alter the method of attack on the disease. The condition of contralateral side is always an important factor in planning the surgical treatment. Recently treatment of pulmonary tuberculosis has taken a new turn, where after the preliminary medical treatment the lesion is removed surgically. More and more segmental resections, lobectomies and pneumonectomies are done with excellent results. But all this cannot be achieved without tomography of the chest which has necessarily to be done at least twice—once before operation to get the exact idea of the nature of lesion and once after completion of treatment to assess the success of the operation, to visualise if any residual lesion still remains. This will make it evident that no treatment of pulmonary tuberculosis is complete without tomograms.

The other most useful application of tomography is in the diagnosis of carcinoma of the lung. This has attracted the attention of the medical profession more and more during the last 10 years. Detailed tomographic studies of such cases where carcinoma is suspected must be made and in many instances one can clearly demonstrate shadows of glandular masses, splaying of the tracheal

bifurcation, partial atelectasis or bronchial stenosis. Almost all these cases do come under observation rather late. The lesion must be detected much earlier to be treated successfully by surgical procedure. Mass photofluorography is the answer for early detection of carcinoma.

In cases of spontaneous pneumothorax of non-tubercular origin, definite diagnosis as to whether tuberculosis is present or not is of paramount importance in planning the treatment. In non-tubercular cases tomograms will show the presence of emphysematous bullae some of which have evidently burst giving rise to pneumothorax. Parietal pneumothorax may not be visible on plain X-rays. This can be demonstrated beyond doubt by tomograms.

In bronchiectasis which shows multiple cavitation it is important to differentiate these cavities from tuberculous cavities especially when bronchiectatic cavitation makes its appearance in the upper lobe. When bronchiectasis is associated with concomitant atelectasis, pneumonia or abscess, it masks the lesion to a great extent. The application of tomography in these cases will show the multiple cavitation and honeycombing, their lobular distribution, and absence of parenchymal lesion in nearby lung tissue. Bronchography also may be of paramount value in differentiating tubercular cavitation from bronchiectatic cavitation. If lipiodol is injected in the bronchial tree and subsequent tomograms taken, it shows their segmental distribution with clarity.

Lung abscess is usually a complication of pneumonia. During the consolidation stage, a uniform dense homogenous shadow is all that is visible on X-ray. The presence of abscess cannot be ascertained until a lighter shadow of gas bubble or fluid level becomes evident with the homogenous shadow. In such conditions tomograms will show the abscess shadow much earlier. This demonstration of the abscess cavity is particularly important when the question arises whether the abscess is benign or malignant in origin. Very often this question can be easily settled by tomography which gives an exact idea as to its prognosis and line of treatment to be adopted. The benign abscess shows an eccentric shadow and fluid level. If the abscess is malignant as a result of breaking down of tumour mass, then the air bubble is usually concentric and there may or may not be any fluid. In addition malignant abscess will show nodular masses of growth projecting into the abscess cavity, and enlarged lymph nodes.

After thoracoplasty everything goes on well for sometime and then suddenly the patient returns with a positive sputum. Apparently nothing can be seen on straight films, because the operated side usually shows a dense shadow of mutilated ribs. Here tomogram will surely show whether the residual cavity is still open or a fresh cavity has appeared, necessitating surgical interference once again. After segmental section or lobectomy the tomograms will show whether any residual lesion is left behind.

Lastly, it must be noted down that this valuable procedure has its limitations and advantage of its usefulness must be fully taken. We are not yet tomography-minded. Economic question should not be the sole factor to avoid its wider use. The amount of additional information it gives in solving many problematical cases fully justifies its wider application. It may not be exaggeration to say that thoracic surgery will be difficult without tomography.

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## RADIOISOTOPES IN THE INVESTIGATION OF PHYSIOLOGICAL PROBLEMS

R. K. Pal

Using the rate of release of  $^{131}\text{I}$ -labelled thyroxine as an index of thyroid activity Brown-Grant has found that (a) the relative activities of thyroxine and triiodothyroxine in repeated daily doses depress pituitary thyrotrophic hormone in the pregnant female rabbits at  $28^\circ\text{C}$  as 1:1.29 (weight for weight), by determining the daily thyroid secretion rate as  $6/\mu\text{g}$  thyroxine/kg body weight (1955a)<sup>3</sup>; (b) oestradiol, oestrone, stilboestrol and hexoestrol, decrease thyroid activity while progesterone and testosterone have no such effect. Progesterone consistently reversed the thyroid inhibition produced by stilboestrol, while testosterone, DOCA, and cortisone did not produce

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this effect consistently and stilboestrol and oestradiol did not alter the response of the thyroid to exogenous thyrotrophic hormone probably due to suppression of TSH secretion (1955b)<sup>4</sup>; (c) exposure to moderate degree of cold increased activity of the thyroid within 8 hr. but with exposure to severe cold there was either no change or a decrease, and after adrenalectomy even moderate cold caused a decrease suggesting that severe cold may act as a nonspecific stress to reduce secretion of TSH by anterior pituitary (1956)<sup>5</sup>; (d) large doses of ACTH, cortisone and hydrocorticosterone reduced the rate of  $^{131}\text{I}$  release in normal rats and rabbits but not in the adrenalectomized ones, of which the last (hydrocorticosterone) appeared to be more effective and roughly as potent as cortisone. Activation of pituitary-adrenal axis by stress (trauma, irritant intraperitoneal injections, etc.) results in inhibition of release in normal and adrenalectomized rats. Small doses of cortisone that have no effect in normal rats produce an increase in  $^{131}\text{I}$  release under such stress (1956a)<sup>6</sup>; (e) ovariectomy in rabbits produces inconsistent effect but coitus and ovulation show no effect so far as thyroid activity is concerned. During the last quarter of pregnancy there was some increase in both the upstroke and release of  $^{131}\text{I}$  and during lactation while the release increased, the upstroke was greatly reduced due to plasma concentration being much higher than in milk M/P 6.7/37.4 (1957)<sup>8</sup> rather than any change in the pituitary TSH secretion and during weaning both returned to their prenatal levels. No correlation, however, existed between stages of oestrus cycle and rate of  $^{131}\text{I}$  release while castration or orchidectomy caused a decrease in the thyroid activity (1956b)<sup>7</sup>.

Collins and Hellman (1955)<sup>12</sup> found a depression of thyroid activity (approx. 50 per cent) in mice (8-21 weeks old) when reared in a hot environment (91°F dry bulb and 85°F wet bulb) as compared to control by injecting 2.5  $\mu\text{c}$ . of  $^{131}\text{I}$ , killing them after 2½ hr. and determining the  $^{131}\text{I}$  uptake.

By a new technique for accurate measurement of  $^{131}\text{I}$  uptake by the thyroid in conscious rabbits Brown-Grant and Gibson (1955)<sup>3</sup> have determined with a collimated scintillation counter the thyroid blood clearance rate to be 1.2 ml whole blood/min, averaging 0.58-0.06 (S. E. of 24 experiments). Hypophysectomy, administration of thyroxine, cortisone and possibly stilboestrol reduced the clearance rate while that of thyrotrophic hormone increased it.

Oddie et al (1955)<sup>22</sup> have tabulated the available information and developed formulae which make it possible to calculate thyroid uptake of  $^{131}\text{I}$  and renal excretion rate from a single observation over thyroid and only one urine assay.

Taplin et al (1955)<sup>21</sup> described a very good test for liver function known as  $^{131}\text{I}$  Rose Bengal Test in which a minute quantity of dye containing 5  $\mu\text{c}$  of radioactivity is injected (I. V.) and the uptake of the dye in either the liver or gall bladder recorded. The test has another advantage of being applicable even in cases of known biliary obstruction.

Brown-Grant and Gibson (1955a)<sup>3</sup> showed that a large dose of radiothyroxine (120  $\mu\text{g}$ ) injected (I. V.) in rabbit disappears more rapidly from the blood. A higher proportion of the dose is deiodinated than after a tracer (1  $\mu\text{g}$ ) dose. Similar patterns of excretion were found for normal and excess amount of endogenously labelled thyroid hormone. On comparison of these findings for man and the rat there appears to be variations in the amount of thyroid hormone excretion in different species. They (1956) again noticed after continuous infusion (I. V.) of 2-4  $\mu\text{g}/\text{min}$ . of adrenaline bitartrate in conscious or anaesthetised rabbits with previous I. V. injection of  $^{131}\text{I}$ , a complete inhibition of the uptake and 16-32  $\mu\text{g}/\text{min}$  of noradrenaline bitartrate were required to produce this effect, which dose of adrenaline was observed to cause a marked vasoconstriction of the thyroid without gross changes in the systemic blood pressure. Insulin (32  $\mu\text{g}/\text{kg}$  body weight) after about 50 min. caused an inhibition of the uptake that was reversed by glucose administration. Surgical trauma also reduced the rate in half the number of animals. So adrenaline from the adrenal medulla probably exerts a marked effect on the uptake of  $^{131}\text{I}$  by the thyroid.

Curt von Euler and Bjorn Holmgren (1956)<sup>14</sup> showed that thyroxine injected locally in the anterior pituitary inhibited the release of  $^{131}\text{I}$  from the thyroid but no effect was there after a local injection into the hypothalamus or median eminence. The release of thyroid iodine in response to exogenous thyrotropine was influenced by simultaneous thyroxine administration. So thyroxine inhibits thyrotrophic secretion by direct action on the anterior pituitary and this is the only route whereby thyroxine regulates thyroid secretion.

The same workers again (1956a)<sup>15</sup> showed that hypophysectomised rabbits bearing pituitary grafts in the anterior chamber of the eye released  $^{131}\text{I}$  at about the same rate as normal controls,

but this release was inhibited by systemic administration of thyroxine, adrenocortical extract and cortisone in the grafted animals which were also not influenced as regards thyroid secretion by exposure to cold environment or submission to stress. This 'feed-back' control of thyroid secretion is not impaired by disconnecting the normal pathways between the hypothalamus and the anterior pituitary. However setting of the 'feed back' system to an adequate level of circulatory hormone seems to be impossible in the absence of normal hypothalamo-hypophyseal connections.

Logothetopoulos and Scott (1956)<sup>20</sup> found after injecting  $^{131}\text{I}$  subcutaneously into pregnant guineapigs and rabbits with or without propyl thiouracil injection 70-80 min. afterwards, radioactivity concentration, F (foetal)/M (maternal) ratio = 1.5/5 at a time when  $^{131}\text{I}$  concentration in mother's circulation was on a rising or steady level. After injection of sodium thiocyanate F/M is less than one. In pregnant rats F/M was not significantly higher than unity but ratios 0.3-0.4 only were found in animals injected with NaCNS.  $^{131}\text{I}$  in foetal or maternal plasma was shown to be present as free iodide ion and the placental transport mechanism for iodide was inhibited by sodium thiocyanate.

By administration of  $^{131}\text{I}$ -labelled thyroxine Frienkel and Lewis (1957)<sup>16</sup> have found that half times for the turn-over of extra thyroidal thyroxine averaged 25 hr. in the shorn and 38 hr. in the unshorn sheep. The enhanced rate of thyroxine degeneration in the shorn sheep was accompanied by significant functional and histological evidence of thyroid hyperactivity; protein-bound iodine in blood, however, remained almost the same in shorn and unshorn groups.

After cannulation of the bile duct and measuring the clearance rate of thyroxine and triiodo-thyroxine labelled with  $^{131}\text{I}$  in bile, Myant (1957)<sup>21</sup> has been able to prove that the liver removes plasma thyroxine more easily when it is bound to the serum proteins by weak bonds than when it is bound by strong bonds and as the plasma concentration rises the binding sites with strong affinity for thyroxine become attached to the binding sites with weak affinity. This explains why the clearance rate rises as the dose is increased.

Hall and Myant (1956)<sup>18</sup> studied the passage of  $^{131}\text{I}$ -labelled thyroxine from mother to the foetus in rabbits by measurement of F/M serum concentration ratio after injecting radiothyroxine in mother and opined that low concentration of radiothyroxine in foetal serum was not due to de-iodination or shortage by the foetus and after an injection in the foetus the concentration in the maternal serum did not exceed 7.1 per cent of that in the foetal serum in 1-4 hr. These results suggest that the tissues between the mother and foetus are almost completely impermeable to exogenous thyroxine up to about 19th day and thereafter they become more permeable as also the foetal thyroid starts secreting thyroxine and hence is the lower concentration of thyroxine in foetus than in the mother.

By injecting 0.05 sec. red cells labelled with  $^{32}\text{P}$  and human serum albumen labelled with  $^{131}\text{I}$  alternately into the axillary veins of a cat anaesthetized with chloralose and measuring the radioactivity in the carotid arterial blood with a scintillation counter and pen recorder, Groom and Rowlands (1957)<sup>17</sup> have found a ratio of different circulation times in plasma and corpuscles to be between 1.12 and 1.2.

Tudhope and Wilson (1955)<sup>25</sup> have very well compared the relative efficiency of R. B. C. with different radioisotopes  $^{32}\text{P}$ ,  $^{86}\text{Rb}$ ,  $^{51}\text{Cr}$  *in vitro* by incubating blood with the isotopes at  $37^\circ\text{C}$  with constant rocking after which the activity of the plasma was measured and the uptake of the isotope by the red cells was calculated. After 3 hr. the plasma was removed, the cells were washed, resuspended in stored plasma and again incubated at  $37^\circ\text{C}$  with rocking. At intervals the radioactivity of the plasma was measured and the leakage of isotopes from cells calculated.

The uptake of  $^{86}\text{Rb}$  at 3 hr. was 33.3 per cent and that of  $^{32}\text{P}$  40 per cent. The leakage of  $^{32}\text{P}$  from red cells was greater than  $^{86}\text{Rb}$  at one, two and three hours—the difference being highly statistically significant. The mean leakage of  $^{86}\text{Rb}$  at 3 hours was 7.8 per cent and that of  $^{32}\text{P}$  was 13.3 per cent. So  $^{86}\text{Rb}$  is a useful agent for labelling red cells and can be used with advantage for measurement of total red cell volume as with similar uptake as  $^{32}\text{P}$ , rubidium label is more stable and possesses  $\gamma$ -radiation so that the distribution of  $^{86}\text{Rb}$  label within the body may be followed by means of an external counter. As compared to this  $^{51}\text{Cr}$  under the same experimental conditions, showed an uptake of 81 per cent in 1 hour and leakage was less than 1 per cent. Although having a disadvantage of requiring a scintillation counter for its measurement it has several advantages as a red cell label too as compared with  $^{86}\text{Rb}$  and  $^{32}\text{P}$ . The uptake of  $^{51}\text{Cr}$

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by red cells is much more rapid and more complete and the label is also very much stable. Read, Wilson and Gardner (1954)<sup>26</sup> have shown that the mean half life of  $^{51}\text{Cr}$ -tagged red cells within the circulation is 26 days whereas that of  $^{86}\text{Rb}$  is 40 hr only. So this prolonged survival of  $^{51}\text{Cr}$ -tagged cells can be utilised to make repeated estimations of red cell volume if injections of unlabelled red cells are given.

After injecting 10-30  $\mu\text{C}$  of  $^{14}\text{C}$ -glucose in pregnant rabbits, Hugget and Morrison (1955)<sup>19</sup> removed the conceptuses  $\frac{1}{2}$ -4 hours later, isolated and purified various materials and measured their radioactivity with Geiger-Muller counter to observe that the placental glycogen in the rabbit is in a state of continuous exchange with the maternal glucose. The glycogen of the decidua and foetal placenta have different patterns of formation. The difference between simple counts shows that the glycogen of the foetal placenta cannot be simply decidual glycogen contained in peninsulae of decidual tissue trapped in the foetal placenta and inseparable by mechanical dissection. If it is decidual glycogen there must be two types of it therein. The rate of formation also varies with the stage of gestation and the variations are not parallel in decidua and foetal placenta. Alexander et al (1955)<sup>1</sup> however, after injecting radioglucose in pregnant sheep found both  $^{14}\text{C}$ -glucose and  $^{14}\text{C}$ -fructose in the foetal blood although there was no hyperglycaemia, which when produced a back flow of glucose from the foetus to the ewe. Reversely in experimental hyperglycaemia the magnitude of glucose flux was over 70mg/min—an amount much less than would be expected on a basis of diffusion. Under physiological conditions the formation and withdrawal of fructose must be in dynamic equilibrium, such that fructose production by a secretory-like process is balanced by its removal or utilisation by the foetus or placenta both. Besides fructose being continuously produced by the placenta the rate of fructose production is constant and independent of glucose concentration in both maternal and foetal blood (Alexander et al, 1955a)<sup>1</sup>.

The view of Wilson and Wiseman (1954)<sup>26</sup> that some fraction of glucose absorbed by the intestines may appear as lactic acid which is smaller *in vitro* than *in vivo*, has been well supported by Pears and Smyth<sup>23</sup> (1956) by estimation of total radioglucose and radiolactic acid obtained from venous blood from an intestinal loop for over a period of 30 min. after introducing  $^{14}\text{C}$ -glucose in low concentration into intestines of dogs anaesthetized with Na phenobarbitone.

Coxon and Robinson (1956)<sup>13</sup> after injection of 2  $\mu\text{C}$  of uniformly labelled C-glucose (I. V) in dogs under phenobarbitone anaesthesia have assessed the relative contribution of particular regions to the overall metabolism by measuring the activity of  $\text{CO}_2$  in the blood (arterial and venous) of hind limbs and expired air. During the first 2  $\frac{1}{2}$  hr after the injection the specific activity of the femoral venous blood  $\text{CO}_2$  is considerably less than the arterial  $\text{CO}_2$ . This gain of  $^{14}\text{C}$ - $\text{CO}_2$  by the limb is explained by the fact that radioglucose is broken to  $^{14}\text{C}$ - $\text{CO}_2$  relatively rapidly in the body and the arterial  $^{14}\text{C}$ - $\text{CO}_2$  thus derived is coming into isotope equilibrium with that in the tissues of the limb during this period. Such equilibrium has been shown to take place after  $^{14}\text{C}$ -bicarbonate injection in dogs.

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**RADIOLOGICAL ASPECTS OF THE CENTRAL NERVOUS SYSTEM—See CENTRAL NERVOUS SYSTEM, RADIOLOGICAL ASPECTS OF THE**

**RADIOLOGICAL ASPECTS OF THE GENITO-URINARY TRACT—See GENITO-URINARY TRACT, RADIOLOGICAL ASPECTS OF THE**

**RADIOLOGICAL CHANGES IN PULMONARY LEPROSY**

*R. Subramaniam*

A short paper of Negre and Fontan deals with 110 patients who had been subjected to routine radiological examination, the examination being repeated within a year and not more frequently. Shadows were seen in the lungs which could be ascribed to tuberculosis and it was considered by the authors as due to leprosy. These cases were associated with lepra reactions. In one case, there was a Trophic ulcer. In all instances the fields were clear and followed up for a year or later. The possibility that some of them may be of allergic nature is considered. Patients may have cutaneous manifestations of undetermined origin which disappear after the reaction subsides and it is suggested that the pulmonary shadows may also be of the same type.

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**RADIOLOGICAL DIAGNOSIS—I**

*P. H. Kronenberger*

Research in various branches of science and medicine has contributed to the spectacular progress of radiology. Since the end of the Second World War many new techniques have been invented: employment of X-rays of higher penetration and of radioactive substances for diagnostic purposes and contrivances for quick change of cassettes, for fluorography, for tomography, for magnification and for image intensification are notable advances. Intravenous and intra-arterial injections of contrast media and catheterization of blood vessels have imparted valuable information in congenital or acquired cardiovascular abnormalities and in various space-occupying lesions. Compact structures in abdomen and mediastinum have been explored by means of retro-pneumoperitoneum and pneumomediastinum. In this review it is attempted briefly to outline some trends in radiodiagnostic methods during the last 4 years, with short references to 200 recent publications.

**Advances in Equipment.**—It is not necessary to dilate on tomography as this procedure has been fully described in another section of this book. Only a few improvements will be related. In 1955 Gajewski and Liese<sup>2</sup> developed a device for simultaneous exposure of 6-7 films at distances of  $\frac{1}{2}$ -1 cm<sup>3,4</sup>. The advantages of this simultaneous tomography are obvious. It saves time for the patient and the staff. The former is exposed to less irradiation, and the life of the X-ray tube is prolonged. The different layers of lungs and heart are visualized during the same stage of respiration and pulsation. This new tomographic appliance can be combined with bronchography in order to achieve a 3-dimensional demonstration of the bronchial tree and it can be used in angiocardigraphy for the study of the pulmonary<sup>24</sup> and systemic<sup>56</sup> circulation or for determination of the blood volume of the heart<sup>3</sup>.

Accurate measurements can be done in laminograms by a simple device introduced by Franke<sup>1</sup>. This "isometer" is used for localisation of foreign bodies, for assessment of site and extension of tumours and other space-occupying lesions and for planning in radiotherapy.

The definition in tomograms can be considerably improved if the X-ray tube moves in 3 instead of 2 dimensions. Devices for this purpose are incorporated in some recent equipments such as the "Polytome" manufactured by Massiot.

Transverse tomography, comprehensively evaluated in publications by Vallebona and by Gebauer,<sup>3,4</sup> is now greatly perfected and simplified. It supplies valuable data in the investigation of lungs, pleurae, mediastinum and the base of the skull. So far it seems the only reliable method to assess size and shape of right atrium without angiocardigraphy. Demonstration of the pancreas, formerly not feasible, can be obtained by transverse tomograms exposed after induction of a pneumo-retroperitoneum. Transverse tomography is practised in various institutions in Europe and America and is also now available in Bombay.

The high voltage and the magnification techniques introduced shortly after World War II are generally accepted as useful measures in certain ranges of applications. They need no discussion in this paper as no new development seems to have taken place in the last four years.



## **Radiological Diagnosis**

The intensification of the fluoroscopic image may gain great importance in future as it permits screening and fluorography of abdomen and even of bony structures with small doses of X-rays. The hazards of genetic effects of irradiation can be greatly reduced if this method is applied for fluoroscopy in hysterosalpingography and other examinations of the abdomen. Furthermore, an accurate positioning can be performed in skull radiography under fluoroscopic control, radioactive substances can be inserted into bony structures under the screen and extensive cinematographic examinations can be carried out without excessive exposure of the patient to X-rays<sup>11</sup>.

It is beyond the province of this paper to dilate on the employment of injected radioactive isotopes as tracers in diseases of the thyroid gland, in brain tumours and in localisation of the placenta<sup>48</sup>.

Inhalation of radioactive Xenon was utilised by Knipping and his associates for the diagnosis of bronchial obstruction. It is achieved by means of Geiger counters which register the irradiation of different parts of the thorax (thoracography)<sup>6</sup> or by the multiplier retina<sup>2</sup>, a very elaborate and complicated equipment which aims at the visualization of the radio-opaque substances within the bronchial tree<sup>5</sup>. Cinematography with the multiplier retina can also be combined with intravenous injection of traces of iodine<sup>131</sup> for the study of heart and peripheral vessels. "Isotope bronchography" and "isotope angiocardiology" may contribute in future to an early diagnosis of lung tumours and cardiac abnormalities and may spare the patient the discomfort and risk inherent in the conventional procedures.

Radioactive isotopes are also used instead of X-ray tubes for routine examination of bones. Mayneord<sup>7,8</sup> produced distinct radiographs of the mandible, maxilla, atlas, elbow joint, tarsals and carpals by means of gamma rays emitted by Thulium<sup>140</sup> and Xenon<sup>133</sup>. This technique is still in an experimental stage, but the initial results are very encouraging. It may become of great importance in examination of accidents, in veterinary surgery and where field work has to be carried out in areas with limited supply of electricity.

Rapid development of radiographs without processing room is available in Picker's "Polaroid"<sup>11</sup> and is of particular advantage in radiological investigations during operations in the theatre. In Xero-radiography<sup>9,10</sup> the rays act on a metallic plate coated with selenium, and the exposed parts are visualized by a photoelectric effect instead of chemical processing. When these new methods are further perfected, radiologists may be able to perform emergency examinations without a bulky portable X-ray equipment and a tent for development. All they need would be a small container with a radioactive element and a handy outfit for processing or a plate with a layer of selenium.

**Improvement in Examinations of Different Parts of the Body.—(a) Circulatory system :** As a rule the right side of the heart and the pulmonary vessels are well surveyed in intravenous angiocardiology. This procedure is, however, not so suitable for the left heart as the longer distance from the brachial vein results in a diminution of the concentration of the contrast medium and a fainter opacification. Two other methods were elaborated for a better assessment of left atrium and left ventricle. They are of particular importance in mitral lesions and certain congenital abnormalities. In selective angiocardiology the medium is injected through a cardiac catheter into the right heart<sup>16</sup> or into the pulmonary artery,<sup>13,21</sup> and a series of films is exposed when the left ventricle or the left atrium is expected to be visualized. In cases of atrial septal defect the catheter may be extended through the foramen ovale into the left atrium or left ventricle for direct injection of the contrast medium into these chambers<sup>23</sup>. In direct cardiac ventriculography the left atrium<sup>15</sup> or the left ventricle<sup>18,22</sup> is punctured and filled with the contrast substance. These methods have so far been tried in a comparatively small number of patients and are not yet free from risk. Lehmann, Musser and Lykens reported, in February 1957, the technique, results and complications in direct cardiac ventriculography and established certain indications and contra-indications<sup>22</sup>.

The incidence of fatalities is still rather high even in conventional angiocardiology, 1-2 per cent. Several methods have therefore been tried to reduce accidents. Pulmonary oedema, the most dangerous complication, could be overcome by intravenous injection of hydrocortisone (Besterman, Leonard and Wood)<sup>14</sup>. Most authors prefer the less toxic acetizoates to the diodo-preparations<sup>18</sup>.

Recently Grosse-Brockhoff, Koch, Loogen, Rotthoff, Vieten and Willmann<sup>19</sup> injected small doses of carbon dioxide and achieved a good visualization of the right heart,

particularly the valves and the pulmonary artery. Preliminary tests ascertained that this procedure is innocuous to patients<sup>20</sup>. The authors, however, caution against employment of this technique before further experience is acquired and recommend it only in selected cases of allergy to iodine.

Demonstration of the pulmonary circulation was considerably improved by Bolt's technique of selective pulmonary angiography. He introduced the catheter into the lobar arteries, the segmental and subsegmental branches, and studied the vascular pattern during the arterial, capillary and venous phases. He found characteristic alterations in various diseases of lungs and pleurae, such as pleural adhesions, atelectasis, pulmonary emphysema, silicosis, tuberculosis and postoperative conditions; furthermore in disturbances of the circulation as infarctions, pulmonary sclerosis, arteriovenous aneurysm and other acquired or congenital abnormalities of heart or great vessels. The data supplied elucidate function and morphology of the pulmonary parenchyma and of the pulmonary circulation and are in many cases of decisive importance as regards the advisability of lobectomy, pneumectomy, decortication, valvulotomy and other operations of the heart and great vessels. Bolt, Forssmann and Rink<sup>24</sup> have recently published a comprehensive description of this technique and an analysis of pulmonary angiograms based on their own experience of 2000 cases<sup>24</sup>. The importance of this procedure in lung disease was also stressed by Cicero and Del Castillo<sup>25</sup> in 1956.

The aorta and its branches are examined after direct puncture or by retrograde approach via the carotid, the radial or the pulmonary arteries. Direct translumbar aortography developed 20 years ago by Dos Santos is well established as a diagnostic method for circulatory disturbances in the abdomen and lower extremities and for evidence of space-occupying lesions. For the thoracic aorta, sufficient evidence is usually conveyed by intravenous angiocardiology<sup>38</sup>. If this examination fails or is not practicable a direct puncture of the thoracic aorta can be attempted either at the apex of the aortic arch<sup>27</sup> or through the left posterior wall above the diaphragm<sup>34</sup>, techniques which are of course more difficult and more dangerous than translumbar aortography.

Even lumbar aortography is not an entirely harmless procedure, and a considerable number of severe accidents have been reported during the last four years by Crawford, Beall, Moyer and De Bakey<sup>26</sup>, McAfee and Willson<sup>32</sup>, Hare<sup>29</sup>, Robinson<sup>35</sup>, Roy<sup>36</sup>, Gaylis and Laws<sup>28</sup>. They observed severe pain, haemorrhages, acute pancreatitis<sup>35</sup>, renal failure, thrombosis of the mesenteric artery, embolism, chylothorax, paraplegia and fatal allergic reactions. In June 1957 McAfee<sup>33</sup> surveyed 12,832 aortographies and commented on the various complications. Numerous suggestions were made by him and other authors to eliminate serious side effects, in particular judicious selection of patients, improvement in technique of injections<sup>37,39</sup> and of anaesthesia, use of less dangerous contrast media<sup>37</sup>, diminution of dose and concentration of the latter<sup>30</sup>, a test film before the injection to ensure correct position of the needle and a follow-up urogram for detection of accidental retroperitoneal bleeding<sup>33</sup>. Crawford, Beall, Moyer and De Bakey<sup>26</sup> are of the opinion that in the great majority of cases of aneurysm, aortography does not need to be performed for purposes of diagnosis or determination of the appropriate surgical approach and should be avoided in view of the inherent risk.

A considerable reduction in dose and concentration of the contrast medium can be obtained in retrograde aortography. It is performed by insertion of a catheter into a peripheral artery, usually the femoral or radial artery, and retrograde movement either by manipulation or by an electric field<sup>54</sup>. Swedish radiologists, particularly Seldinger, Edholm and Oedman, elaborated special devices for percutaneous puncture of the femoral artery instead of the more dangerous surgical exposure<sup>43,51</sup>. They used a special instrument with a polyethylene catheter which can be moulded in hot water with the effect that its tip fits to the orifice of the renal artery or the coeliac axis. Whereas the Swedish authors prefer the femoral approach for visualization of the renal circulation, De Nunno<sup>50</sup> selects the radial artery for this purpose.

These procedures are technically difficult, time-consuming and not always successful, but they seem to be less dangerous than direct aortography. Nevertheless, Edling and Helander<sup>41</sup> recorded at the Carolinska Hospital five instances of severe impairment of the renal function in 320 retrograde arteriograms, 8 cases of renal damage have been reported from Swedish hospitals by Alwall, Johnsson, Tornberg, Werko<sup>41</sup>, and one case of renal failure by Dormandy, Joekes and Sutton<sup>42</sup>. The authors stress that these examinations should only be carried out on strict indications and after careful investigation of the renal function by various tests.

## Radiological Diagnosis

Retrograde femoral arteriography was also advocated for the demonstration of the pelvic circulation in cases of uterine fibroids, adnexal tumours, extra-uterine pregnancies<sup>45</sup> and for localisation of the placenta<sup>43,55,184</sup>.

Oedman<sup>52</sup> and Sutton<sup>53</sup> achieved a very good visualization of the thoracic aorta by retrograde arteriography after percutaneous puncture of the carotid, the radial or the femoral artery. These techniques are, however, not free from risks. Abrams<sup>40</sup> who surveyed 1706 retrograde thoracic aortographies, reported 29 fatalities. He found the carotid approach particularly dangerous and recommended several methods to reduce the hazards.

As a rule, Kemp-Harper<sup>31</sup> prefers direct aortography as the retrograde route is more difficult, more time taking and more prone to failures and complications. On the other hand, Gregg, Allcock and Berridge<sup>46</sup>, Hare<sup>47</sup>, Murray and Tresidder<sup>49</sup> are of the opinion that this method is less risky and provides more information as regards the condition of the aortic branches.

Cerebral arteriography initiated 30 years ago has now reached a high degree of reliability and safety. It should be performed by an experienced neurologist or preferably by a team of neurosurgeon and radiologist. Segelov<sup>60</sup> encountered no complications in 660 examinations except for an occasional skin rash, and Sedzimir<sup>59</sup> reported an uneventful course of 273 cerebral angiographies. The authors described their technique and attributed the absence of accidents to proper preliminary medication, good local or general anaesthesia, adequate intervals between injections, and small doses of non-irritating contrast media. Acetrizoates were proved to be more innocuous than the previously used diodo-preparations<sup>60,62</sup>. Dimant, Moxon and Lewtas<sup>57</sup> in reviewing 1536 angiograms state that this method may be hazardous in arterial hypertension and arteriosclerosis, but in increased intracranial pressure it is safer than encephalography or pneumoventriculography. In cases of haemorrhage, intracranial aneurysm and angioma they found it of paramount importance for the surgical management and observed that the findings were positive in 88 per cent of space-occupying lesions in which the vascular pattern provided valuable supplementary evidence. A correct localisation was feasible in 74 per cent.

Simultaneous tomography mentioned in a previous chapter was used in cerebral angiography by Chatton, Pelissier, Barjon and Temple<sup>56</sup>. They claimed that due to effacement of overlying bony structures the passage of the carotid artery through the petrous pyramid and the communicating arteries can be better visualized and that the pedicle of an aneurysm may be seen in tomograms of the appropriate plane.

The technique of vertebral angiography, important for evidence of space-occupying lesions in the posterior fossa, is presented by Segelov<sup>60</sup> and Lindgren<sup>58</sup>. The following approaches are possible :

1. Direct percutaneous puncture or surgical exposure of the vertebral artery.
2. Retrograde catheterisation *via* the radial, the subclavian or the femoral artery. Lindgren prefers the direct percutaneous puncture and if it fails, he employs the retrograde route *via* the left femoral artery. Sheldon<sup>61</sup> devised a special needle for puncture of the vertebral artery which precludes the chances of dislodgement and facilitates rapid injection of the dye.

Considerable progress was also made in the visualization of the venous system. Phlebography of the lower limbs can be carried out by the following approaches<sup>63</sup>: 1. retrograde phlebography *via* the femoral vein, 2. ascending, from the dorsum of the foot, 3. *via* a varix, 4. *via* a popliteal vein, and 5. *via* the tuberosity of the 5th metatarsal or some tarsal bone (transosseous phlebography). Greitz<sup>64</sup> indicated techniques of special positioning for visualization of the venous circulation of the leg.

Abdominal phlebography supplies important data in cases of obstruction of the inferior vena cava or of compression of abdominal vessels by an adjacent space-occupying lesion. It is performed by the ascending route from the femoral vein or by direct puncture of the vena cava<sup>66</sup>. Demonstration of the renal veins may be indicated in cases of nephrosis, presence of large veins of the abdominal wall, oedema of the lower trunk, in recurrent pulmonary infarction and renal tumours. It can be obtained by insertion of a catheter into the saphenous, iliac or brachial veins or by direct injection into the inferior vena cava<sup>74</sup>.

Intra-osseous phlebography is now frequently employed. The direct communication of the sinusoidal circulation of the bone marrow with the systemic circulation permits a useful way for the visualization of the venous outflow and of major veins in the vicinity of the bones. Opaque

media can be injected into the calcaneus, the tibia, the greater trochanter, the pubic rami, the iliac crest, the spinous processes, the ribs or the sternum. A detailed description of the pertinent techniques can be found in recent publications of Petrakis, Steinbach and Gilfillan<sup>71</sup>, Lester and Lampe<sup>69</sup>, and Susse<sup>75</sup>.

Trans-osseous phlebography is the method of choice when veins are not visible or accessible, for example in oedema of the limbs<sup>66</sup>, or if the competence of deep-seated veins has to be explored prior to operations. It is furthermore of assistance in the assessment of healing of fractures and in the investigation of various bony lesions which are associated with alterations of the venous circulation such as osteitis, leukaemia and bony tumours.

The importance of trans-osseous phlebography in diseases of the pelvis was stressed by Rabaiotti<sup>72</sup>. A group of French authors described interesting changes of the circulation in osteo-arthritis of the hip joint<sup>70</sup>. The thoraco-abdominal veins were visualised by injection of dye into the spinous processes in cases of mediastinal and retroperitoneal tumours and lesions of the vertebrae<sup>63</sup>. Injection of contrast substance into the sternum provided demonstration of the internal mammary veins which showed characteristic changes in cases of secondaries of breast cancer, findings which indicated or ruled out the necessity of resection of retrosternal glands<sup>67</sup>.

Complications seldom occur in intra-osseous phlebography<sup>75</sup>. Osteitis, haemorrhages, localised inflammation of soft tissues, thrombophlebitis or pulmonary infarction were occasionally reported<sup>69</sup>.

A large number of papers have been published about splenography. The injection of the contrast medium into the spleen provides a good demonstration of size and course of splenic and portal veins, a definite differentiation between intrahepatic or extrahepatic obstructions and indications as regards the possibility of anastomosis with the inferior vena cava. The patency of postoperative anastomosis can be well assessed. In many cases it presents the best method of visualization of oesophageal or gastric varices and reveals secondaries or areas of non-functioning parenchyma in the liver. The current literature and technique has been recently surveyed by Bergstrand<sup>77</sup>, Gvozdanovic & Hauptmann<sup>84</sup>, by Rodriguez<sup>85</sup>, by Catalano and Giardiello<sup>82</sup>, by Evans and O'Sullivan<sup>83</sup>. These and other authors<sup>79,86</sup> point out that it is advantageous to take a series of films at intervals of  $\frac{1}{2}$  to 2 seconds.

Splenography though reasonably safe, is not completely without risk. The following complications were observed: pain at the site of the injection or the left shoulder, nausea, headache, increase or drop of blood pressure, tiredness for some hours, impairment of liver function, rise in temperature and allergic reactions. More serious accidents may be caused by severe haemorrhages, the rupture of the spleen or faulty injections into the stomach or peritoneal cavity. Aurig<sup>76</sup> and Bruwer<sup>81</sup>, therefore, recommend to carry out the splenography immediately prior to the planned operation.

If puncturing the spleen is unsafe on account of the reduced clotting power of the blood, the portal vein may be visualized at laparotomy and injection of the dye into the jejunal, the gastric or epiploic branch<sup>80</sup>. Bierman recently attempted direct subcutaneous puncture of a radicle of the hepatic veins for demonstration of the portal circulation and was successful in 64 of his 73 patients<sup>78</sup>.

(b) *Urinary tract*: In urography the diodone and iodoxyl preparations were greatly replaced by new contrast media, the sodium monoacetrizoates Urokon<sup>109</sup> and Diaginol<sup>89</sup>, the methylglukamine monoacetrizoate Fortombrine, the diacetrizoate Hypaque sodium<sup>104</sup> and Urografen<sup>102</sup>, and sodium diprotrizoate Miokon<sup>87</sup>. These preparations are less toxic and provide a good visualization of kidneys and ureters in a high percentage of cases. Several comparative studies were made as regards the quality of the newer contrast media. There is a slight divergence of opinion, possibly on account of difference of methods and conditions of investigation. Most authors state that the diacetrizoates are somewhat better tolerated than sodium monoacetrizoates<sup>87,93,98,99,100,107</sup>. Lentino, Zeitel, Jacobson and Poppel<sup>100</sup> mention that Urografen shows less side effects than Hypaque sodium, but is more difficult to inject on account of its greater viscosity. Eyer, Drew and Bohne<sup>93</sup> found the same rate of allergic reactions in both these drugs. As regards pictorial effects it appears doubtful whether there are any significant differences between the various new media. The opacification of renal sinuses and ureters can be considerably improved if 30 c.cm are injected instead of 20 c.cm. The dose of 30 c.cm can be

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easily administered without appreciable risk to the patient at least as regards Hypaque sodium. This was pointed out by several authors<sup>94, 100, 101, 104, 107</sup>, and observed also in our series of 95 cases<sup>\*\*</sup>.

The usual restriction in intake of fluid can be relaxed with the new contrast media. Cave, Rankin and Mabbs<sup>90</sup>, and Esch and Halbeis<sup>92</sup> showed that the visualization of the urinary tract can even be improved in elderly patients if they drink 100 to 250 c.cm of water prior to the injection.

Subcutaneous injections of Hypaque sodium were found to be relatively painless and of advantage in urography of infants<sup>91</sup>.

A number of side effects including one fatality were recorded also with the newer drugs, though they occur considerably less frequently. In this respect, the recent survey of 3,831,850 urograms by Pendergrass, Hodes, Tondreau, Powell and Burdick<sup>105</sup> deserves full attention. On the strength of their observations they recommend various measures for prophylaxis and treatment of toxic reactions. Youngblood, Williams and Tuggle<sup>112</sup> advise an emergency kit consisting of a throat gag, forceps, suction apparatus, oxygen, syringes with hydrocortisone ready for immediate intravenous injections, benadryl, chlortrimeton and adrenalin. Winter<sup>111</sup>, Vechsler<sup>110</sup>, Simon, Berman and Rosenblum<sup>108</sup>, Lapidés and Boyd<sup>97</sup> suggest simultaneous intravenous injection of contrast medium and antihistamines and Robinson advocates a prophylactic administration of dramamine<sup>109</sup>. Pendergrass<sup>105</sup>, however, cautioned against intravenous injection of antihistamine preparations as they may provoke adverse effects and is rather in favour of oral doses of Trimeton.

Moeckel noticed relaxation of contracted calyces after injection of 'Buscopan' in 128 of 190 cases<sup>103</sup>. He used this drug in descending and ascending pyelography for the differentiation between spasm and organic narrowing.

Hydrogen peroxide added to the contrast medium causes foam formation when in contact with bleeding surfaces. This procedure was recommended by Klami<sup>96</sup> in ascending pyelography to detect early tuberculosis or small renal tumours.

Casey<sup>88</sup> obtained good pyelo-ureterograms in advanced cases of hydronephrosis by percutaneous puncture of the kidney and direct intrarenal injection of the contrast medium.

Acetizoates in combination with a lubricating jelly (Lubafax) or with a thickening agent (Thioxocone) were introduced for cysto-urethrography<sup>95</sup>.

(c) *Biliary Tract* : In oral cholecystography the tri-iodo compounds, such as Telepaque and Trilombrine (iopanoic acid)<sup>137</sup>, Teridax (iophenic acid)<sup>138</sup> and Biliodyl (phenobutiodil)<sup>125</sup> have been widely substituted for older preparations. Their side effects are mild and practically negligible<sup>142</sup>. They permit a better visualization of the gall bladder and especially of the extrahepatic ducts. Using Telepaque, Mosca<sup>134</sup> was able to trace the biliary ducts in 82 per cent of his cases by exposure of films 8, 12, 15 and 30 minutes after fatty meal ; Grugan<sup>121</sup> in 91 per cent ; Sarasin and Thommen<sup>141</sup> even in 97 per cent by combination of iced saline lotion and fatty meal and exposures after 5, 10, 15, 20, 30 and 45 minutes. Reynolds & Fulton<sup>137</sup> obtained a demonstration of the ducts in 58 per cent of the patients even with a single exposure after 20 minutes.

The excellent results of the intravenous cholecystography<sup>113</sup> are already well known and do not need to be emphasized in this paper. A good visualization of the biliary tract is still possible with this method even when the gall bladder has lost its power of concentration as the injected Biligradin is excreted by the liver into the extrahepatic ducts.

After cholecystectomy it is possible to visualize the biliary ducts by the oral as well as by the intravenous method. Twiss, Gillette, Beranbaum and Poppel<sup>149</sup> have elaborated a special technique consisting of a double dose of Telepaque and employment of opiates and achieved visualization of the ducts in many cases. Their finding was confirmed by Lowman, Davis and Lawson<sup>130</sup> and by Hanssen and Deeb<sup>122</sup>. It appears, however, that in postcholecystectomy cases, the intravenous method is easier to apply and provides more frequently a delineation of the ducts (Teschendorf)<sup>147</sup>.

<sup>\*\*</sup>We are greatly indebted to Winthrop (U.S.A.) and Dey (Calcutta) for their kind supply of ampoules of 30 c.cm Hypaque sodium.

Many authors have evaluated the oral and intravenous methods<sup>115, 117, 118, 123, 124, 126, 127, 128, 129, 135, 141, 145, 146</sup>. There appears to be a consensus of opinion that they are not competitive, but complementary<sup>114</sup>. Either of them has its merits. The oral cholecystography is less toxic and supplies more information as regards the ability of the gall bladder to concentrate the dye. Several cases are known in which cholecystitis or presence of stones were revealed by the oral and missed by the intravenous technique<sup>114, 118, 123, 145</sup>. The latter, on the other hand, is occasionally superior in the visualization of the gall bladder and the biliary ducts, particularly the hepatic ducts. It has the disadvantage of a greater risk to the patient though severe reactions are comparatively rare.

Several authors have reported serious side effects such as collapse of the peripheral circulation<sup>113, 115, 132</sup>, profuse vomiting<sup>132</sup>, and exfoliative dermatitis<sup>150</sup>. Theander found in 500 intravenous cholecystographies 39 early or late complications, in four cases collapse, in others oedema of face, urticaria, lacrimation, coryza with sneezing, protracted nausea, vomiting, biliary colic, provocation of attacks of angina pectoris and epilepsy<sup>148</sup>. In this country Sethna<sup>143</sup> met with no serious side effects in his series of 74 cases. In the meanwhile, however, at least 3 cases of collapse have also occurred in Bombay (personal communications of Drs. Athle, Gole and Krishnamurthy). Most authors agree<sup>114</sup> that as a rule the oral method should precede the intravenous for determination of the gall bladder function. The following indications are mentioned for intravenous cholecystography: (1) the post-cholecystectomy syndrome, (2) if the patient is unable to swallow, to retain or digest the tablets on account of a disturbance of the gastro-intestinal tract, (3) if the examination has to be carried out in a very short time, particularly if in emergency cases an affection of the gall bladder and biliary ducts has to be ruled out as a cause for the clinical symptoms, (4) if the gall bladder was not visualized by the oral method, (5) if the differential diagnosis between cholecystitis and cholelithiasis cannot be made in the oral cholecystograms, (6) if a detailed study of the ducts is required prior to operation, particularly for an assessment of the hepatic duct or for evidence of a calculus in the common duct, and (7) for confirmation of a stone suspected in oral cholecystography. Recently Shehadi<sup>144</sup> summarized most of the relative indications and contraindications for oral and intravenous cholecystography.

Mitchell combined a simultaneous oral and intravenous examination and claimed to have obtained an optimal visualization of gallbladder and biliary ducts<sup>133</sup>. His observation of calculi within extra-hepatic ducts in 6 per cent of his cases speaks for the accuracy of this technique.

Sangster<sup>140</sup> advocated a contraction of the sphincter Oddi by injection of morphine in order to ensure a more persistent filling of the biliary ducts. Exposure of radiographs in different views under fluoroscopic control<sup>136</sup> and laminography<sup>116</sup> were employed to eliminate overlapping of the biliary ducts by intestinal gas.

The new oral and intravenous drugs were used successfully in infants<sup>151</sup>; furthermore in cases of obstructive jaundice if they are at a stage of regression and the icteric index is not higher than 12 and the bilirubin below 1.7<sup>139</sup>; and in mild or moderately advanced cases of hepatic cirrhosis provided there is no impairment of the renal function and no cardiac insufficiency<sup>119, 131, 143</sup>.

Operative cholangiography which supplies the most detailed visualization of the biliary tract, particularly also of the hepatic ducts, was considerably improved in recent years. Brown<sup>154</sup>, Block and Orloff<sup>153</sup> have abandoned the direct puncture of the common biliary duct in favour of the introduction of a polyethylene catheter. Wall & Peartree<sup>157</sup> surveyed the results of 444 operative cholangiographies and pointed out the possible source of error in technique and interpretation.

Radiologists have learnt to eliminate injuries to the pancreas and the liver by using a moderate amount and low concentration of the new contrast media.

McClenahan<sup>132</sup>, Don and Campbell<sup>120</sup> and Wise and O'Brien<sup>152</sup> stated that in post-cholectomy cases the width of the biliary ducts and the transit time in passage of the contrast medium do not always convey completely reliable data for a block in the region of the sphincter Oddi on account of the great variations under normal conditions and as the dilatation of the duct persists after removal of the obstacle. Various French authors developed a better technique for the assessment of the function of the gall bladder and biliary ducts by a combination of operative cholangiography and manometric measurements. This procedure has been introduced as a

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routine measure during gall bladder operations in some European countries. An interesting survey of these studies was supplied by Hess<sup>156</sup>.

(d) *Pancreas*: The demonstration of the pancreas silhouette by means of retroperitoneum and transverse tomography is mentioned in a previous chapter<sup>3</sup>.

The internal structure of the pancreas was recently explored by Doubilet, Poppel and Mulholland<sup>155</sup>. They inserted a plastic tube through the duodenum into the ampulla of Vater before the injection of a contrast substance. They found characteristic alterations of the duct pattern in acute pancreatitis, pseudocysts and true cysts. They are of the opinion that this method can be easily performed and may convey valuable diagnostic data in these diseases.

(e) *Lungs and mediastinum*: Contrast media suspended in oil may remain within the pulmonary parenchyma after bronchography and then lead to lipid pneumonitis and fibrosis. 3 methods were suggested to preclude these complications. (1) Admixture of sulphonamide and talcum to Lipiodol or other oily contrast media in order to inhibit the entrance into the alveola<sup>166,167</sup>. These thickened preparations permit a very good coating of the bronchial tree, but under pathological conditions they are occasionally retained within the lung and cause foreign body granulations (Delaloye)<sup>159</sup>. (2) Employment of water-soluble contrast substances such as Ioduron-B, Perabrodil-M, watery Dionosil, Propylidol and Xumbradil, which are easily absorbed. During bronchography they disappear, however, very rapidly from the bronchial tree into the periphery. Furthermore, they often cause irritation to the mucous membrane resulting in cough and bronchial spasm. Their current status was recently assessed in a paper by Niknejad, Aurelius, Peterson and Rigler<sup>168</sup>. (3) Use of iodine compound dissolved in arachis oil such as Dionosil oily. They are absorbed within a few days and appear to be less irritant and slower in their passage through the bronchi than the water solutions. For these reasons many authors prefer contrast substances of this type<sup>160</sup>, but opinions are still divided in this respect.

Priviteri<sup>170</sup> and Nordenstroem<sup>169</sup> advise deep inhalation during bronchography in order to achieve an adequate distribution of the opaque medium throughout the lungs and Gianturco and Miller<sup>161</sup> use this method for rapid bilateral bronchography.

Lupacciolo<sup>167</sup> recommended stereoscopic films during bronchography for good 3-dimensional visualization of the bronchial tree. It is also now feasible to combine simultaneous tomography with bronchography for demonstration of bronchi at different layers<sup>3,4</sup>.

Liese, Mertin, Fruhmahn and Klun<sup>164</sup> introduced a special spatula for bronchography of the central portions of the lung. It is particularly indicated in elderly or severely ill patients on account of its easy application. The various "over the tongue" methods are, however, not always adequate for detailed visualization of the segmental and subsegmental divisions of the bronchi and are given up by most radiologists in favour of introduction of the dye by special Metras catheters<sup>172</sup>. Strnad designed a catheter which is particularly suitable for the purpose as its tip can be tilted in such a way that it fits into the lumen of the lobar or segmental bronchi<sup>165,171</sup>.

Leh<sup>163</sup> advocated general anaesthesia and withdrawal of the bulk of the contrast medium through the catheter after completion of the examination. He obtained with this method a very rapid and complete bilateral survey of the bronchial tree. Radiographs exposed with general anaesthesia have the advantage that bronchial spasm is eliminated and a detailed filling of the segmental bronchi can be achieved.

Direct injection of opaque medium into cavities of the lungs for study of position and extension was carried out by Beatty<sup>158</sup>.

The pneumomediastinum was introduced as early as 1936 by Italian clinicians, particularly Condorelli and his associates<sup>174</sup>. They injected air into the anterior mediastinum by puncture above the sternal notch or into the posterior mediastinum by the transtracheal route. Later on Rossi<sup>174</sup> recommended radiographs of the thorax following induction of a retroperitoneum as the air enters both the anterior and the posterior mediastinum in this way. This procedure can be easily carried out and aids in the differential diagnosis of pleuromediastinal adhesions, mediastinitis, mediastinal tumours, enlargement of lymph glands or thymus, acquired or congenital deformities of the heart or great vessels and in pericardial diseases. The results were recently evaluated by Tapiovaara<sup>173</sup>.



Strnad and his associates<sup>162</sup> studied the peristalsis of the oesophagus in inflammatory or neoplastic lesions of the mediastinum by means of kymography and found characteristic alterations. Subsequent operations proved that these two conditions could be differentiated and presence and extension of secondary malignancies be predicted with a high degree of accuracy.

(f) *Salpingography*: It is generally agreed that opaque oils are not free from risk on account of oil metabolism or foreign body reactions. They were, therefore, abandoned by many radiologists and replaced by water-soluble preparations which contain carboxyl-methyl cellulose for greater viscosity, such as Ioduron-S<sup>179</sup>. Later on it was observed that these solutions are also prone to produce painful foreign body granulomas<sup>175</sup>. Because of this occurrence, other contrast media were advised, especially Salpix<sup>177</sup>, a solution of diodone in polyvinyl pyridone, and Perjodal H in which an acetizoate is dissolved in dextran<sup>176</sup>. Foreign body reactions were subsequently reported also with these 2 new compounds though less frequently and less extensive<sup>181, 184</sup>. To reduce inflammation, Johnsson<sup>180</sup> added streptomycin and penicillin to Perjodal H. Finally, highly concentrated solutions of Radioselectan which is chemically identical with Urografin<sup>183</sup> and of Biligrafin<sup>182</sup> were recommended without addition of thickening agents. O'Driscoll<sup>178</sup> and Sandler<sup>185</sup> however, encountered pain and peritoneal irritation in Biligrafin salpingography. It appears therefore doubtful whether a completely safe contrast medium has been found as yet.

(g) *Gastro-intestinal Tract*: The superiority of the modern non-flocculating contrast media is generally recognised and was recently stressed in India by Patterson in his studies of the small intestine<sup>200</sup>.

The examination of the appendix, already facilitated by the employment of Alubar<sup>196</sup>, was further improved by addition of carboxyl-methyl cellulose as shown by Busch, Chrom & Guldberg<sup>188</sup>.

In selected cases solutions of Urokon and Hypaque were used instead of barium<sup>189, 191, 192, 193</sup> for demonstration of the mucosal pattern and small ulcers of stomach and duodenum; furthermore they were used in cases of perforation, intussusception and intestinal obstruction in which administration of barium is impractical or contra-indicated. These examinations are of particular importance for the differential diagnosis between mechanical obstruction and physiological ileus. It goes without saying that these iodine compounds which were administered only in doses of 25 to 150 c.cm are far too expensive for complete filling of the stomach or intestines.

Klami, Gianturco and Miller<sup>194</sup> added hydrogen peroxide to the barium swallow and noticed that the foam produced by contact with blood aided in the diagnosis of ulcerations at the lower end of the oesophagus and cardiac portion of the stomach.

The technique of air insufflation which is generally employed for polypi and other interluminary tumours, was improved by Moreton, Stevenson and Crozier<sup>190, 199</sup>. They introduce a small amount of barium into the descending colon and force it into the transverse and descending portion by inflation. More recently Welin and his associates<sup>186</sup> modified the double contrast enema by employment of Veripaque and tannic acid, and Andren & Frieberg<sup>187</sup> described a new technique for visualization of polypi in the rectum and sigmoid loop which they claim to be more informative than sigmoidoscopy in some cases.

The demonstration of the mucosal relief of the colon is often incomplete with the conventional technique of evacuation and air inflation, especially in instances of disturbed motility. McLaren and Copland<sup>198</sup> obtained an improvement of the mucosal pattern by adding Veripaque to the barium enema and by taking films at the moment of evacuation. Henderson<sup>195</sup> was disappointed with the results of this method and preferred a combination of ethyl-methyl cellulose and barium. We attained a very satisfactory detailed visualization of the mucosa by another method, namely the administration of a minimal amount of barium and exposure of spotfilms under fluoroscopic control prior to the routine enema. This technique was described by me in a preliminary paper at the Indian Congress of Radiology in 1956<sup>197</sup> and further experience with 150 cases will be published presently.

**Summary.**—During the last four years improvements in equipment, contrast media and technique of application have considerably enlarged the scope and usefulness of radiodiagnostic examinations. Some of the newer procedures are not completely free from risk, but several measures were undertaken to prevent and remedy serious side effects or accidents.



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Radiographs could be obtained without the X-ray tube and the processing room. New avenues were opened for isotope angiocardiology and isotope bronchography by means of injection of traces of Iodine 131 or Xenon 133, procedures which are completely safe and cause no discomfort to the patient.

The methods of investigation in the urinary, biliary, respiratory and gastro-intestinal tracts were perfected and augmented. Selective pulmonary angiography, trans-osseous phlebography and splenography advanced beyond the experimental stage. The shape and structure of the pancreas, formerly inaccessible to X-rays, can henceforth be explored by direct and indirect methods.

"To-day there is no longer an organ, no matter how deeply hidden it may be or how inaccessible it may appear, which may not become a tributary to the learned art of radio-diagnosis. The rays which pass through it reveal in transient or durable images the secret of its form, its movements, its structure and its lesions" (Antoine Beclere).

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## RADIOLOGICAL DIAGNOSIS-II

M. G. Varadarajan

### Pulmonary Diseases

**Tropical Eosinophilia:** This is one of the common pulmonary disorders in India. Basu (1954)<sup>6</sup> in a study comprising 137 cases has described his observations. Mottling in the lung fields is frequent and may be coarse or fine. It is polymorphic and not so well circumscribed or dense as in miliary tuberculosis. Very fine mottling often gives rise to a misty appearance. In some cases a small area of crowding of bronchovascular shadows has been seen while the rest showed fine scattered mottling. With treatment the discrete mottling disappears but the localised crowding persists. Bronchography done in a few cases showed no abnormality. The extent of the radiological findings does not appear to be correlated with the severity of symptoms or with the eosinophil count.

**Kartagener's Syndrome:** A triad of transposition of viscera, bronchiectasis and sinusitis constitute a syndrome, named after Kartagener, (1933)<sup>25</sup>. So far about 104 cases have been described in the literature in which the three cases reported in the Indian literature have not been included. They are by Chatterjee (1951)<sup>13</sup>, Baruah and Chari (1952)<sup>5</sup> and Raman et al (1955)<sup>11</sup>. In the case reported by Baruah and Chari, besides the triad there was an associated bronchogenic carcinoma.

Sanjivi, (1957)<sup>43</sup> has observed eight cases not yet reported. A case of this syndrome has been reported by Varadarajan (1957)<sup>50</sup> in a boy aged 17.

Devadatta (1957)<sup>16</sup> reports a case of this syndrome in which the middle and lower lobes on the left side were resected; the case was observed for one and half years after discharge. He was symptomless and in excellent general health after the resection.

**Cystic Disease of the Lung:** Except for echinococcus and dermoid cysts, the aetiology of cystic disease of the lung is not often entirely clear. The condition may be either acquired or congenital. Some cysts of the lung are the sequel of an inflammatory process and others are entirely noninflammatory. They may be either bronchial or parenchymal in origin, single or multiple and they may contain fluid, gas or both. With the recent advances in radiological diagnosis and in the surgical management of pulmonary cysts, a good deal of attention is recently being focussed on the subject of cystic disease of the lung. Shah and Nair (1957)<sup>44</sup> in their article on cystic disease of the lung stated that the incidence of this disease, from June 1952 to May 1955 was 18 during this period at the K. E. M. Hospital, Bombay. The over-all incidence of cystic disease of the lung works out approximately to

## Radiological Diagnosis

one in four thousand cases of pulmonary disease among indoor patients. One is inclined to feel that if a proper look-out is kept, the incidence should perhaps be much higher. Most of the cases were detected in the second decade, the youngest being 17 years old and the oldest 50 years.

Larkin and Philips<sup>27</sup> have stated that "the possibility of malignant degeneration in the wall of a cyst forms another indication for removal of these cysts whenever feasible". Winthrop Peabody, Sol Katz and Edgar Davis (1957)<sup>52</sup> have reported a case in which serial Roentgenograms taken over a 33-month period furnished good proof of the origin of an undifferentiated bronchial carcinoma from a long-standing lung cyst.

Peabody et al (1957)<sup>53</sup> in an article entitled "Bronchial carcinoma masquerading as a thin-walled cyst" state that the rather singular ability of bronchial carcinoma to mimic the Roentgenographic manifestations of almost any benign pulmonary lesion is well-known. This was not always appreciated of course, as witness the once prevalent practice of dismissing any unexplained or unresolved pneumonitis as viral in origin, any round circumscribed density as a tuberculoma and any cavitary infiltration as tuberculosis—all lesions in which the malignant potentiality has become adequately documented. However, there remains another disguise behind which a carcinoma can hide, one to which infinitely little attention has been paid, namely the thin-walled pulmonary cyst. A case has been presented by him to illustrate this point and thereby attention is called to the hazard in dismissing every cystic pulmonary lesion as benign.

*Hydatid Disease of the Lung*: Hydatid disease is of relatively frequent occurrence in the temperate regions where climate plays an important role and in places (e.g. the Middle East) where dog host of the adult tapeworm (*T. echinococcus*) is a constant companion of man. Till recently hydatid disease was considered uncommon in India. Reported cases of hydatid disease however bear very little relation to the real incidence of the infection. Though the dog is not such a close companion of man in India as in Europe or Australia, dog's excreta contaminating water, food and vegetables, whether directly or through the agency of flies suffices to pass the disease on to man. Betts and Thomas (1956)<sup>7</sup> consider that hydatid disease is endemic in India.

In India few cases of pulmonary hydatid disease have been reported. Betts (1956)<sup>7,8</sup> has observed three cases; Billimoria has also reported three cases (1956). Hydatid cysts when they occur are usually found in the liver. The proportion of pulmonary to hepatic hydatid appears to vary in different countries. There are no comparable figures in our country. Betts (Vellore)<sup>8</sup> feels that the incidence of pulmonary hydatids compared to hepatic hydatids is much higher at Vellore than is reported elsewhere in India.

Contributions on this subject have been made by Nazareth (1957)<sup>34</sup>, Gadekar (1955)<sup>21</sup> and Madan Lal Aggarwal (1956)<sup>29</sup>; the latter two have contributed mainly to the radiological appearances. Nazareth has reported a case of pulmonary hydatid disease in a six year old girl, the diagnosis based mainly on X-ray appearances of the cyst in the lung, despite a negative Casoni's test.

It is worthwhile considering the radiological aspects of hydatid disease of the lung in two parts:

1. *Before establishment of a communication of the cyst with a bronchus.*
2. *After a communication is established between the cyst wall and the bronchus.*

1. *Before a communication with the bronchus is established*: A hydatid cyst casts a round or an oval shadow which is uniformly dense and sharply outlined. The surrounding lung parenchyma is normal. When the cyst is compressed by the chest wall, the mediastinum, or a fissure, it loses its round appearance. The cysts are usually single in the lungs and often occur in the posterior part of the right lower lobe, although any part of a lung may be involved. Sometimes multiple cysts are met with. A small solitary hydatid casts a round shadow which has the appearance of a "coin shadow". Sometimes the cysts are oval or even lobulated. If fluoroscopy is done these cysts may show a change in shape during respiration. This is known as "Escudero-Nemenow sign". But, this sign merely tells the observer that the opacity is cystic and nothing more. Calcification of the lung hydatid is said to be rare but when it does occur it is fairly typical of it; it takes on a curvilinear or a circular appearance.

A large solitary round opacity having a sharp outline is usually due to a hydatid cyst, although such a shadow is seen in cases of a solitary, "cannon ball" metastasis, particularly from a testicular growth the presence of which is quite obvious or can be easily discovered.

2. *Appearances after communication with a bronchus*: To understand these appearances it is essential to know the pathological anatomy of the hydatid cyst. Madan Lal Aggarwal<sup>29</sup> has described it well. Communication of the adventitia of a hydatid cyst with a bronchus brings about a series of very characteristic changes which produce radiological appearances which are pathognomonic of hydatid disease.

(a) When communication with a bronchus is established air enters the space between the adventitia contributed by the lung of the host and the ectocyst and rising to the top forms a crescentic or sickle shaped air cap.

(b) It is not appreciated that quite a large amount of air may sometimes collect on the top of the ectocyst and the ectocyst may be pushed so much downwards as to be flattened so that it resembles a fluid level and an erroneous diagnosis of a fluid-containing cavity or a lung abscess may be made.

(c) A hydatid cyst with a large air cap may press on the bronchi leading to degeneration, infection, and consolidation of the surrounding lung. The consolidation obscures the cyst and in the X-ray picture the air cap resembles a cavity in a consolidated portion of the lung. When the inflammation of the surrounding lung resolves on treatment, the hydatid cyst with an air cap reveals itself. This phenomenon has not been recorded before.

(d) When the hydatid cyst ultimately ruptures, the watery fluid present in it leaks into the surrounding air-containing adventitial cavity and/or is coughed out and air enters the cavity of the cyst itself which maintains its round or oval appearance for a considerable time. Thus an unmistakable sign of "cavity inside a cavity" develops. The lower part of the inner cavity may be immersed in fluid when its curved upper margin separated by an air cap from the upper curved margin of the pericyst gives the "double arc" sign. When the inner cavity is fully submerged in the fluid in the outer cavity, its wall may shine as a ring through a fluid of lesser density or it may be completely obscured by opaque fluid in the pericyst. A possibility of hydatid disease must be considered in a case of a localised "hydropneumothorax".

The fluid may be completely expectorated when the empty hydatid cavity is seen to lie loose in an empty pericyst. These two gradually shrink in size till they form a very small mass which does not give any further trouble to the patient. After rupture the hydatid cyst may collapse into a heap which floats on the top of the hydatid fluid which leaked into the pericyst. The appearance has been compared to a water lily called "Camellotte" which floats on the surface of South American rivers and the appearance produced is known as the "Camellotte sign". These collapsed hydatids may be expectorated leading to spontaneous cure. The expectorated cysts resemble grape skins. The expectorated hydatid fluid has a salty taste.

### Alimentary System

*Enteroliths Associated with Tuberculous Intestine* : Enteroliths are on the whole relatively uncommon and those of the bile acids and other constituents of bile are even rarer. Only a few cases are recorded in the literature and except in the case reported by Kelly (1932)<sup>20</sup> there was no tuberculous lesion of intestine in the other cases. Majority of them occurred in a diverticulum chiefly in the duodenum and jejunum as reported by Watson (1924)<sup>5</sup>, Shaw (1940)<sup>46</sup>, Armitage (1950)<sup>4</sup>, Robinson (1953)<sup>42</sup> and Slater (1953)<sup>45</sup>. Enteroliths are rarely associated with strictures of the intestine. A case is recorded of multiple enteroliths associated with multiple strictures of the ileum due to tuberculosis in a woman aged 25 by Chaudhuri (1957)<sup>14</sup>.

Biochemical analysis of two of the stones showed mineral matter, mainly calcium, from the outer crust but the inner zones of the stones consisted of bile acid salts with a small proportion of bile pigment, cholesterol and fatty acids.

*Spleen* : Percutaneous splenoportal venography utilising rapid serial Roentgenography.—Lately, the treatment of portal hypertension has become mainly surgical. For effective surgical intervention, a proper preoperative visualisation of the splenic and portal veins is very helpful.

There are two methods of visualizing the portal system. (1) Portal venography developed by Blakemore and Lord (1945)<sup>9</sup> and later modified by Moore and Bridenbaugh (1951)<sup>32</sup> and Child and associates (1951)<sup>12</sup>. This method has the chief disadvantage of being restricted to the operating room. The examination is possible only after the incision has been made and the abdomen opened. This eliminates any flexibility in choice of incision. Furthermore, this technique does not usually provide complete coverage of the portal venous system.

## Radiological Diagnosis

(2) The second method is the percutaneous splenoportal venography first described experimentally in the dog by Abeatici and Campi (1951)<sup>102</sup>. This method provides an excellent means of visualising the portal system prior to operation. It is a simple, safe technique and prevents the possibility of many hours of fruitless search for a nonexistent or thrombosed vein. Despite these advantages the method has received only limited clinical application. Evans and O'Sullivan (1957)<sup>19</sup> have carried out this procedure on 41 patients and Umapathy (1957)<sup>48</sup> in 19 patients. They conclude that in the surgical management of portal hypertension the method of percutaneous splenoportal venography provides invaluable preoperative information regarding the integrity of the portal circulation and the diagnostic quality of the examination depends chiefly on the expertness of splenic puncture.

The technique adopted by Umapathy is briefly described here. In ascitic patients tapping is first done and the splenomegaly is confirmed. Calcium is given by mouth and vitamin K parenterally for about a week prior to the test. One day previous to the test one c.cm of the contrast medium is given intravenously to test sensitivity. The patient is also taught to take a deep breath and to hold it for about a minute. He is prepared as for an intravenous pyelography so far as enemata, diet, etc. are concerned. One hour before the test, 15 mg of morphia is given intramuscularly. He is laid on his back on the X-ray table, over a three cassette changer centered beneath the transpyloric plane, with the upper and lower parts of the body supported on pillows. It is explained to the patient that he may experience peculiar sensations in the abdomen which may vary from warmth to actual pain and that he should not move his body. The exact site of puncture is determined by the relation of the enlarged spleen to the costal border (bigger the spleen, lower the puncture). About 2.5 cm is estimated to be the thickness of the structures from skin to the splenic capsule and depending on the size of the spleen, the depth of the puncture into it is adjusted to between 5 and 7.5 cm. The needle is plunged in the direction of what might be the centre of the enlarged spleen. The dye is injected as quickly as possible and when the last 5 c.cm is still in the syringe, X-ray exposures are commenced and three pictures are taken in quick succession. Seven minutes later, another X-ray is taken which usually shows the intravenous pyelographic effect of the dye. If any renal or ureteric abnormality is noted, further X-rays are taken. This information is particularly useful when splenorenal shunt is contemplated. A careful watch is kept for two more days to forestall any delayed rupture of the spleen.

Cooper et al (1953)<sup>15</sup> claim that this test could be done also to show intrahepatic space-occupying vascular lesions and also to show the relationship of portal vein to retroperitoneal masses like cancer of the head of the pancreas.

Du Boulay et al (1957)<sup>18</sup> state that the preoperative splenic injection method reveals only one aspect of the portal circulation. To obtain complementary information at laparotomy, injection of radio-opaque dye into a jejunal vein or into the portal vein itself with X-ray studies are necessary. They claim that only thus a composite and complete picture of the portal blood flow can be obtained. They point out that with this procedure alone, deceptive appearances and their faulty interpretation are likely.

**Liver:** Congenital herniation of the liver—The occurrence of a partial eventration of the diaphragm has attracted little attention. It is not at all a rarity. It is remarkable for its virtually exclusive occurrence on the right side and its predilection for the anteromedian portion of this hemidiaphragm. Its radiological picture is sufficiently characteristic to allow the correct diagnosis to be made with certainty from the appearance alone.

Recognition of this condition by physical examination is virtually impossible. Dullness to percussion and diminution of breath sounds at the right base anteriorly may conceivably arouse suspicion as to the presence of such a condition but the ultimate clinical diagnosis must depend upon fluoroscopic and radiological study.

Six cases have been collected in a period of less than one year by Alfred Vogl and Allan Small (1955)<sup>3</sup>. A case has been discovered exclusively by Roentgenography by Varadarajan and Ramathan (1957)<sup>40</sup> in a male aged 59, whose main complaint had been vague pain over the precordium, unrelated to exertion.

## Skeletal Disorders

**Osteoclastoma:** Temporal bone—This arises usually from the epiphyseal ends of the long bones. Osteoclastoma arising from the skull apart from the jaw is rare (Lord and Stewart) (1943)<sup>28</sup>. Records of the Johns Hopkins Hospital for 35 years show only 22 cases of osteoclastoma

in the skull, 14 in the mandible, six in the maxilla and two in the rest of the skull—both of them in the sphenoid. In an article by Reddy (1953)<sup>22</sup> has reported 96 cases of osteoclastoma examined in the Madras Medical College, over a period of ten years, of which 13 occurred in the maxilla and mandible. The other bones of the skull were not involved. In the series reported by Shrivastav and Sharma (1954)<sup>47</sup>, out of 15 cases over a period of four years, nine cases were of the long bones, five of the jaws and one of the skull bone.

Very few cases of osteoclastoma from the temporal bone have been reported in the literature. A case of osteoclastoma of the right temporal bone is reported by Shrivastav and Sharma (1954)<sup>47</sup>. This totals to seven on the whole. In this case the tumour was confined to the external auditory meatus in a female, aged 28.

**Osteoclastoma of the skull**—This is a rare condition. Only ten cases have been reported in the available literature. Ramamurthi, Viswanathan and Pillai (1954)<sup>37</sup> report a case of osteoclastoma of the sphenoid bone simulating a pituitary tumour, in a male aged 35, with a complaint of headache and gradually increasing dimness of vision and for the last month, he had not been able to lift his right eyelid.

Positive neurological findings were: (1) primary optic atrophy of the right and temporal pallor of the left optic disc; (2) complete loss of vision in the right eye, with contraction of temporal field of vision in the left eye; (3) limitation of medial and upward movements of the right eye, whereas external rotation of the eye was not limited, and (4) ptosis of the right eyelid. Roentgenogram of the skull showed enlargement and erosion of the pituitary fossa.

Pathological report stated that the bony destruction was from an osteoclastoma. In this connection it is worth bearing in mind that radiologically, giant-cell tumours of the skull bones show sharply demarcated areas of bone destruction and not the typical soap-bubble appearance that is seen in the long bones.

**Osteitis Deformans or Paget's Disease** : This disease is common in the West especially in the United Kingdom but very rare in this country. But the disease in its typical form has been recorded in Madras by Menon (1955)<sup>30</sup>. During the three years, 1950-1953, he has observed nine typical cases of Paget's disease.

**Gargoylism** is characterised by heavy repulsive facies, kyphosis, distension of the abdomen with enlarged liver and spleen and mental deficiency. Clouding of the cornea is also often present, though it was absent in almost a fifth of the cases reported. A case has been reported by Prasad (1953)<sup>36</sup> in a child aged two and half years.

Ramamurthi (1954)<sup>38</sup> has reported three patients with gargoylism. The first was a male, aged 14, with a complaint of difficulty in walking, kyphosis and protuberant abdomen. The liver and spleen were not palpable. X-rays of the spine showed typical changes of chondro-osteodystrophy of the Morquio-Brailsford type.

The second, a female aged 6 years was referred for mental deficiency. This case had some spots of opacity in the cornea and the spleen was palpable; X-rays of her spine showed typical features of gargoylism.

The third patient, a female aged 15 years, was brought for mental deficiency. Her facial features were characteristic. She also had hypertelorism. There was kyphosis with enlarged liver and spleen. There was no corneal opacity. Her intelligence quotient was far below normal. X-rays of the spine showed features of gargoylism.

The radiological features are interesting and characteristic. Gargoylism is considered as an atypical form of chondro-osteodystrophy (Morquio-Brailsford). Though there is a general resemblance to chondro-osteodystrophy, it has distinct differences of its own.

According to Caffey<sup>10, 11</sup> an uneven increase in the growth of the shafts of the long bones is the most important single diagnostic feature in the skeleton of a patient with gargoylism.

In the vertebrae, differences can be made out. In gargoylism the upper and lower surfaces of the vertebral bodies are convex so that they present a circular rather than a quadrilateral outline (Fairbank)<sup>20</sup> whereas in chondro-osteodystrophy the vertebrae are flattened out or biconcave with a tongue-like process projecting from the front. In addition, in cases with well-marked kyphosis in gargoylism, one vertebral body may be smaller than the rest and may show beaking.



## Radiological Diagnosis

**Osteopetrosis with Hypertelorism and Syndactylism<sup>30</sup>:** Osteopetrosis is an anomaly of osteogenesis of unknown origin though there is a definite familial tendency. Radiologically almost all the bones of the skeleton show excessive density with thickening of the cortex and narrowing of the medullary canal. All biochemical investigations have proved normal.

Hypertelorism was a term introduced by Greig (1924)<sup>23</sup> to describe a wide separation of the two eyes with a widening of the nasal bridge. He established that this condition was due to an enlargement of the lesser wing of the sphenoid bone which may be caused by many conditions. This may rarely occur in osteopetrosis.

Association of syndactyly with osteopetrosis is very rare. There has been only one report of syndactylism associated with osteopetrosis. Higginbotham and Alexander, in 1941<sup>21</sup> reported four cases of osteopetrosis in one family of which three, showed syndactylism. There has been no other report of this association in the available literature.

A case with the following features has been reported by Ramamurthi and Pillai (1956)<sup>38</sup> in a female, aged 29, who complained of deafness of six months' duration with a four months' history of headache preceding the deafness.

**Morquio's Disease<sup>33</sup>:** In 1928, Morquio described the cardinal manifestations of a familial osteochondrodystrophy characterised by: (1) dwarfism; (2) deformities of the bones of the trunk and extremities; (3) Roentgenological changes characterised by absence of centres of ossification, destruction, rarefaction and proliferation involving all the bones of the body except possibly those of the skull; it has since come to bear his name. Since its first description by Morquio, this disease has been observed in most European races as well as, other races. To 71 cases reported in the literature, Misra (1957)<sup>31</sup> adds one case of Indian origin, a female child, aged four and half years. A case of this disorder diagnosed in 1942 and followed up for thirteen years, has been recorded by Varadarajan in a male, aged 14, at the time of diagnosis (1955)<sup>40</sup>.

**Bone Changes in Leprosy:** Patterson (Vellore) (1956)<sup>35</sup>, from a study of 116 leprosy patients during a period of four years, describes three types of bone changes in leprosy.

1. Specific destructive changes, due to lepra reaction and due to leproma formation in bone. Lepra reaction is a condition in which there is a violent tissue response in leprosy. It can be local or general. It does not give rise to immune bodies, and it can occur more than once in the same patient. The most striking and the most permanently disabling bone changes can occur during a severe lepra reaction in the fingers.

(a) In a mild lepra reaction, there may be minimal bone destruction with pseudo-cyst formation only.

(b) In a more severe lepra reaction, a very violent bone-destructive process widely expands the cortex.

(c) In most cases however, the bone-destructive process involves mainly the subarticular, more vascular part of the bone and there is resultant collapse of the articular surface and resultant "cupping" deformity of the joints.

(d) In some cases lepra reaction in the soft tissues gives rise to some subperiosteal bone erosion. This erosion may be concentric in the form of a ring or eccentric on the anterior of lateral surface of phalanx with or without joint subluxation.

Even in the absence of any history of lepra reaction, (a) lepromatous cases often show pseudo-cyst formation or honeycombing in the subarticular part of the metacarpals and phalanges (17.5 per cent in this series); (b) enlarged nutrient foramen (17.5 per cent in this series); (c) a tubular formation of the shafts of metacarpals and metatarsals in the bones of children due to the specific action of the lepra.

2. Non-specific bone-destructive and bone-erosive changes due to the presence of secondary infection in hands and feet where there is sensory loss.

3. Osteoporotic changes due mainly to disuse.

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## RECONSTRUCTIVE SURGERY—See PLASTIC AND RECONSTRUCTIVE SURGERY

### RECTAL PROLAPSE, SURGERY OF

M. Chaudhuri

**Rectal Prolapse.**—In recent years valuable contributions have been made by several authors on the various aspects of the prolapse of the rectum.

Berglas and Rubin (1953) in their interesting work by X-ray myography of the levator ani muscle have shown the function of this composite muscle in relation to the pelvic viscera. The latter were visualized by barium emulsion in the rectum and vagina at the same time. It was observed that in the erect position in the female with a normal pelvis, the rectum and vagina lie in an almost horizontal position upon the levator plate or raphe shown by myography. They also showed that with diminished tone the levator plate becomes more oblique and along with it the position of the rectum is also altered in a more vertical plane, and therefore, with increased intra-abdominal pressure herniation of the pelvic viscera is liable to occur. This study was mainly done for cases of uterine prolapse but it also holds good for the rectum. Muir (1955) confirmed these findings by myography using diodone with hyalase injection into the puborectalis muscle through the ischio-rectal fossa. The old concept founded on Moschowitz's view that the defective pelvic fascia is responsible for a prolapse is no longer correct. Moschowitz's operation was based on this fact and invariably gave poor results. Although his idea led to other improved methods such as Graham's operation in which not only the fascia but the levator muscle is also repaired per abdomen. Munsif (1952) recommends Graham's operation for complete prolapse. He reported 31 cases, in four of those Graham's operation was done

## Rectal Prolapse, Surgery of

with better results as compared with the other six cases on whom recto-sigmoidectomy by Miles' method was performed.

*Recto-sigmoidectomy*: Miles' modification of Mikulicz's operation is the common method used all over the world but the recurrence with or without incontinence is frequent as the pelvic floor is not repaired. Miles had advised high suturing of the peritoneum to the emerging bowel, but it does not actually alter the depth of the recto-vaginal pouch. Gabriel (1948) improved on it by suturing the adjoining edges of the pubo-rectalis after closure of the peritoneum. He has had excellent results in 30 out of 38 followed up cases of recto-sigmoidectomy, improved results in 3, and recurrence in 5. But Hughes (1949) while reviewing 150 cases of recto-sigmoidectomy for complete rectal prolapse in the St. Mark's Hospital, London, found recurrence in 60 per cent of 108 followed up cases, and even in those 40 per cent in whom prolapse had not recurred, 21 out of 43 patients were incontinent in varying degrees. Goligher (1951) in his Hunterian lecture attributed it to the removal of the sensory region of the rectal ampulla causing sensory incontinence. Those with patulous anus and poor sphincter tone are more prone to develop incontinence following this operation even though they may be continent pre-operatively. This has also been observed in cases of rectal carcinoma where restorative resection of the rectum involves the ampulla. It is therefore, an important consideration while deciding on the length of the rectal stump that should be left behind during recto-sigmoidectomy by Miles' method or by other resection methods per abdomen. In the former operation Miles had suggested that the incision for resection of the rectum should be half an inch distal to Hilton's line; Ewing (1954) however, does not consider this a very accurate marking. Moreover, it would mean removal of almost the entire rectal ampulla, which is to be avoided in the light of Goligher's observation. However, recto-sigmoidectomy operation still has its place in the treatment of complete rectal prolapse mainly in those subjects unfit for abdominal operation.

In recent years Thiersch's operation has gained popularity. Gabriel (1953) recommends it for anal incontinence as well as for minor degrees of prolapse of the rectum, particularly, in the elderly frail subjects or in mentally defective or deaf patients who are unable to co-operate to do sphincter exercises post-operatively, and are not suitable for major operations. He has described in detail the methods of insertion of silver wire of 19 or 20 standard wire gauge on a Doyen's needle stressing that the anal orifice should be tightened sufficiently enough so as to allow the index finger comfortably in the anorectal lumen to avoid the risk of faecal impaction. He used the method on 25 patients for primary anal incontinence, secondary anal incontinence following recto-sigmoidectomy or Moschowitz's operation, and for incontinence following anal trauma with success. He considers it suitable for selected cases with patulous anus and minor degrees of prolapse. More recently McPherson (1956) has reported the results of Thiersch's operation on 11 cases, 2 were mentally deranged and one had tabes dorsalis, all did well although in a few instances the wire had to be reinserted but the end result was good. This simple procedure is undoubtedly very effective in selected cases with poor sphincteric tone on whom major operative intervention is contraindicated.

One often encounters difficulty in maintaining the prolapse within the anal orifice in badly neglected cases. Very often such cases are also psychologically affected and it is difficult to get their co-operation. The pre-operative preparation for major procedures therefore, becomes prolonged and unsatisfactory. Cooper (1952) described an original idea of pre-operative internal splinting for such cases with a wide bore rubber tube which is passed into the rectum after reduction of the prolapse so that it is an inch longer than the actual prolapse. The tube is anchored at the anus by 2-3 silk sutures and is maintained in the rectum for about a week. This allows the passage of flatus and faeces and the patient is made more comfortable. This temporary measure helps to improve the local condition and thus the patient is made fit for a major operation.

Various forms of plastic repairs have been described from time to time by different authors. Roistein (1952) used fascia lata graft for massive rectal prolapse by abdominal approach to reinforce the anterior support of the rectum at the level of the recto-vesical pouch with good results in 4 cases.

Recently Muir (1955) made very valuable contribution in his presidential address to the Proctology Section of the Royal Society of Medicine. His approach to the problem is from quite a different angle. He observed that following the operation of anterior resection of the rectum for rectal carcinoma, formation of excessive dense adhesions resulted in the perirectal region

fixing the rectum to the sacrum firmly, so that the abdomino-perineal excision of the rectum for recurrence of the growth became very difficult. This led him to think of the possibility of using anterior resection as a method of treatment for complete rectal prolapse. He reported his results of operation on 8 cases with very good results and no recurrence, the longest follow-up was for 6 years. He stresses that the rectum should be mobilised properly down to the levator ani muscle, laterally and posteriorly, and that the peritoneum forming the pouch of Douglas should be dissected off the posterior vaginal wall and excised. The rectum is divided across leaving a distal stump of 3 inches in length, and the upper rectum together with the slack part of the sigmoid colon is resected, followed by an end to end anastomosis. This is certainly a more radical approach than any of the other methods. Muir however, considers that recto-sigmoidectomy still has its place in the treatment of complete rectal prolapse especially when abdominal operation is not indicated. Goligher (1956) refers to Muir's method "as a most important contribution to our knowledge of this difficult condition". In time this operation may replace older methods, since the risks of resection of the rectum and colon by trans-abdominal route are considerably reduced with the advent of new antibiotics, modern methods of anaesthesia and better knowledge of management of such cases. Butler (1954) suggested combined abdomino-perineal approach for recto-sigmoidectomy and reported good results of operation in 5 cases. Hughes (1957) advocates synchronous combined abdomino-perineal repair for the treatment of complete prolapse of the rectum. The procedure is much simplified as two surgeons operate at the same time; one operates on the abdomen, mobilises the rectum and repairs the fascial plane while the levator ani is repaired by the perineal route. In his latest publication Goligher (1958) recommends the Roscoe Graham type of operation for the treatment of complete prolapse of the rectum. He describes in detail the modified technique of the operation and emphasises three essential steps: exclusion of the deep pouch of Douglas, repair of the pubo-rectales muscles, and thorough mobilisation of the rectum thus causing perirectal adhesions. He records his experience on 23 patients over the past 7 years with no operative mortality, and has had excellent functional results in 15 patients, 4 showed improvement, and 4 had complete incontinence.

The cases of prolapse in children are mainly treated conservatively and on the whole the results are good. Spontaneous cure may also result (Thompson, 1956). The condition seldom recurs once it is corrected properly. Irani (1953), however, prefers operative treatment to conservative methods. He recommends Lockhart-Mummery's operation of proctopexy, to fix the rectum to the sacrum by packing the postrectal space with gauze to encourage adhesion formation. He reported on 45 cases treated by this method with only one recurrence. He also favours a simpler method, the linear cauterization of prolapsed rectal mucosa in suitable cases. The latter is sufficient in majority of the cases who do not improve with conservative treatment. Proctopexy does seem a major procedure for children, the commonest cause unfortunately in our country is malnutrition causing lack of supportive tissue, and as these infants and children commonly suffer from diarrhoea, simple medical treatment and adequate nursing care of these cases cure the condition. It is true that this sometimes requires a prolonged stay in the hospital, but it is worthwhile since with the growth of the child the sacral curve also develops and supports the rectum posteriorly. In these cases the pelvic hiatus is seldom affected except in the process of general atonia of the muscles due to malnutrition and anaemia.

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## Renal Tubular Acidosis

REGIONAL ILIITIS—See Under GASTRO-INTESTINAL TRACT, TUBERCULOSIS OF

## RENAL TUBULAR ACIDOSIS

J. B. Mehta

This is a condition seen chiefly in children but cases in older children and adults have been reported. An infant previously doing well, apparently fails to thrive, vomits, has marked constipation, is irritable, dehydrated, hypotonic and develops acidotic sighing breathing. The urine is, however, alkaline or neutral. In fact an alkaline urine in the presence of signs of acidosis, and a dehydrated child without obvious evidence of loss of fluids is the cardinal paradox that points to the diagnosis. Blood chloride and urica are raised<sup>2,4</sup>. Serum calcium, proteins and other blood chemistry findings are normal. Renal calcinosis is present in about a third of the cases<sup>4</sup>.

The aetiology of the disease is not clear. As a result of a defect of reabsorption of the sodium bicarbonate by the renal tubules, the plasma alkali reserve falls and excessive quantities of bicarbonate are excreted in the urine. Carbonic anhydrase inhibition has been blamed. Different portions of renal tubules excrete urine at different pH values of the blood. Carbonic anhydrase is required for the reabsorption of the bicarbonates. The proximal portions excrete smaller quantities of bicarbonates and require little of the enzyme reaction. As the distance of the tubules from the glomeruli increases, the amount of plasma bicarbonate that could be effectively reabsorbed with the aid of carbonic anhydrase is raised. If carbonic anhydrase enzyme reaction is blocked then the more distal tubules (where there is a higher concentration of bicarbonates) cannot reabsorb the bicarbonates which are in turn excreted in the urine<sup>3,4</sup>.

Cases in adults have been reported and are always associated with osteomalacia and renal calcinosis<sup>1,2</sup>.

Prognosis is good in the infantile variety as the treatment is simply to overdose the child with alkalis or Sohl's solution (10 per cent sodium citrate and 6 per cent citric acid), though recovery may take months. Recovery is permanent unless it is associated with hypercalcaemia, calcinosis, or other renal tubular dysfunction.

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## REPRODUCTION, PHYSIOLOGY OF

R. K. Pal

Sen, et al (1956)<sup>18</sup> estimated the amounts of different important constituents of guinea pig's semen collected by electro-ejaculation and found that the average values of protein and ascorbic acid varied between 8 to 12 per cent and 4 to 8 per cent respectively in the whole semen. As the major portion of the guinea pig's semen is the seminal vesicular secretion, the acid phosphatase (6-13 units per 100 g) was found to be invariably lower than the alkaline phosphatase content (28-42 units per 100 g).

Mann (1954)<sup>11</sup> is of opinion that testosterone is required by the seminal vesicles for the production of fructose, citric acid and other chemical constituents of the vesicular secretion and distribution of water in the gland. After injection of testosterone propionate in castrated rats Rudolph and Stearns (1954a)<sup>15</sup> found that extracellular water content of the seminal tissue was reduced about threefold almost to the value of 13.8 per cent found in normal noncastrated rats ; the rate of respiration of the tissue from rats thus treated was also affected, and increased by about 30 per cent to the level of the vesicles from normal rats (1954b).

The movement of different ions between the secretions of the seminal vesicle mucosa of the guinea pig and physiological saline after incubation under various conditions has been studied by Breuer and Whittam (1957)<sup>3</sup> who found that the figures for Na, K and Cl in the fresh mucosa were 33.5 $\mu$ , 102.5 $\mu$  and 46.5 $\mu$  mol/g tissue respectively whereas those for the secretion were 13.5 $\mu$ , 1.6 $\mu$  and 11.1 $\mu$  mol/g tissue respectively. After aerobic incubation at 37°C, there were high

K and low Na concentration gradients in the tissue than glucose alone. Anaerobic incubation showed about the same concentration of Na and K as aerobic, probably due to an adequate energy supply from high anaerobic glycolysis of the tissue. The concentration gradients were reduced aerobically by DNP and anaerobically by sodium fluoride. Potassium of the seminal vesicle mucosa exchanged completely with blood plasma potassium *in vitro*. The tissue potassium exchanged with the same rate both aerobically and anaerobically.

Hopkinson and Kerby (1955)<sup>9</sup> have studied the interaction of insulin, oestrone and progesterone on the metabolism of isolated uterus from ovariectomised rats and have found that the rate of glucose uptake and lactic acid production was higher than that of the muscle. Addition of insulin to the medium increased the rate of glucose uptake of both muscle and mucosa without affecting the rate of lactic acid production. Twentyfour hours after injection (S. C.) of progesterone the rate of glucose uptake was increased, addition of insulin *in vitro* further increased the rate but after an injection of oestrone on addition of insulin *in vitro* there was no longer a significant rise in the rate of glucose uptake, which however, was decreased after 36 hours of the injection. Addition of oestrone or oestradiol *in vitro* did not affect the glucose uptake.

Schofield (1955)<sup>17</sup> studied the behaviour of the uterine muscle under the effect of injected or naturally secreted oestrogen and progesterone and the results were similar to those previously observed *in vitro*. Progesterone-dominated uterus developed less tension than the oestrogen-dominated uterus, when these were related to the weight or length of the segment. Progesterone has a latent period, i.e., the period of time after the injection when the character of the muscle contractility begins to change from oestrogen-dominated behaviour in about 21 hours. Harken et al (1957)<sup>8</sup> found that although there was no significant change in the total collagen content of the uterus during the oestrus cycle, treatment of spayed rats with oestrone and progesterone individually and in combination produced collagen formation in the uterus, which was delayed and slight as compared to the growth in weight and non-collagenous protein.

Elcoate et al (1955)<sup>5</sup> produced zinc-deficiency in weaning rats on a diet containing less than 0.5/ $\mu$ g per Zn/g within 5-8 weeks and along with restricted growth, alopecia, greying of the black hair and skin lesions, they found in sections of the testis and epididymis (histologically) no sperms. All the male sex organs, e.g., testes, epididymis, seminal vesicles, prostate and coagulating glands were much smaller than normal but animals fed on deficient diet with a daily supplement of 100 mg of zinc had normal sexual organs and normal sperm production. When Zn-deficient rats were given testosterone propionate there was temporarily a slight gain in body weight and although the weight of the testes declined, the tubular degeneration was arrested and there was an increase in the weight of the epididymis, seminal vesicles and prostate, suggesting that the failure of growth in accessory sex organs in Zn-deficiency is due to decreased testosterone propionate.

Biggers et al (1956)<sup>3</sup> have found that addition of natural or synthetic oestrogens or some of their conjugated forms caused proliferation of the vaginal epithelium with stratification and keratinisation in the tissue culture. This change is a characteristic feature of the response of ovariectomised mice to either the systemic or local administration of oestrogens and the same response identical in all main features has been found in the vagina of immature mice after subcutaneous injection of oestrone. The effective dose of oestrogen in tissue culture is considerably lower than that required to produce response in ovariectomised mice.

Gupta (1957)<sup>6</sup> is of opinion that Indian male frogs (*Rana tigrina*), which are according to Bhaduri and Bardhan (1949)<sup>1</sup> and Mukherjee and Saha (1952)<sup>13</sup> suitable and economic animals for use in pregnancy diagnostic tests, cannot be utilized all throughout the year, as the histological appearance of their testes reveals seasonal variations in their spermatogenetic activity in the form of mature spermatozoa, on which the validity of the test entirely depends.

Hand (1957)<sup>7</sup> has observed in children that changes caused by a failure of the testis to descend *per se* does not impair fertility and so it is best to defer hormone stimulation in such cases until the age of eight. Nissim (1957)<sup>14</sup> has proved definitely that following degeneration of the seminiferous tubules after nitrofurazone (a cytotoxic agent) given to mice in concentration of 0.15 to 0.3 per cent in the diet, the interstitial cells of the testes undergo true hypertrophy. Similarly cryptorchidism with ligation of epididymis may result in greater testicular atrophy than serotal invagination, but the mean weight of the seminal vesicles does not differ significantly. When the results of the two methods are combined, the significance of values are markedly increased

## Retrolental Fibroplasia

( $P < 10^{-20}$ ). Mann (1956)<sup>11</sup> however, believes that the increase in the interstitial cells is only apparent and attributes it to the collapse of the tubules.

Dott and Walton (1956)<sup>4</sup> measured the sperm fertility of semen of ram and bull in relation to metabolism and showed that anaerobic glycolysis is not the sole source of energy for sperm movement and that respiration also played an important part. The maximum motility was obtained when both glycolysis and respiration were operating together. Luktuke and Bhattacharya (1957)<sup>10</sup> have correlated the sperm concentration and rate of fructolysis in semen samples from 7 hill bulls and 5 Hariana bulls and have made the following observations : (1) There is a highly significant linear correlation between the sperm concentration and fructolysis, and (2) initially fructose content and sperm concentrations were increasingly correlated, and so they suggest that by the use of 'fructose utilisation test' it is possible to detect any deterioration in semen quality (for artificial insemination) which might pass unnoticed on microscopical examination.

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## RETROLENTAL FIBROPLASIA

T. B. Gupta

**Introduction :** Retrolental fibroplasia is one of the diseases which has attracted the attention of a large number of workers since it was first described by Terry in 1942 and in the last 15 years, large numbers of articles have been published on this subject. Terry who coined the term "Retrolental Fibroplasia" wrote as follows : "The development of embryonic connective tissue in the meshwork of the persistent hyaloid artery system behind the crystalline lens as a result of improper development of the inner eye, usually developing 3 to 5 months after birth in the extremely premature infant, is a disease which I call 'Retrolental Fibroplasia'". Terry associated the disease with prematurity and suggested that retrolental fibroplasia was due to a persistence and overgrowth of the hyaloid system. As a result of large amount of work by different workers in this field, the original suggestion of Terry has been totally changed and the conception of the disease as it stands today, is quite different. In the following lines I have tried to present a brief summary of our present knowledge of retrolental fibroplasia.

**Definition :** Ashton defines retrolental fibroplasia as a primary retinal disease of non-inflammatory origin resulting from disordered retinal vascularization.

**Incidence :** It is difficult to give a general statement of the incidence of the disease, for reports indicate that it varies from country to country and from place to place in the same country, American writers have quoted the incidence as 7 per cent (Owens & Owens, 1949a ; Gilger, 1949); in infants of 4½ lb or less at birth (Terry, 1945), 15 to 20 per cent (Owens & Owens, 1949a), and 23 per cent (Clifford & Weller, 1948) in those of less than 3 lb at birth. From Australia, an incidence of 15 per cent in premature infants in Melbourne is reported by Campbell (1951), and from Paris, an incidence of 7.5 per cent is quoted by Leolong and others (1951). It is clear from the above that this disease has become today an important medical and social problem. In the United States of America, for example, it is now regarded as the major cause of blindness in children below school age. As far as our country is concerned, no reliable data about the incidence of the disease is available.

As indicated above, there is considerable evidence to show that the incidence of the disease increases as the birth-weight of the baby decreases. King (1950) followed the original series



of Terry (1945), and found that of 238 cases of retrolental fibroplasia, all were under 5 lb at birth, 85 per cent were under 4 lb, and 44 per cent under 3 lb. In Great Britain, Moffat (1950) found that 4 out of 12 babies blind from the disease had a birth-weight of under 3 lb, and the remaining 8 had birth-weights of 3 and 3½ lb. In King's series of 238 cases, there were 52 sets of twins and 2 sets of triplets. Among them, the disease developed in one twin in 18 sets and both twins in 8 sets, while one twin in each of the remaining sets, died. Apart from its occurrence in twins, where prematurity is probably the causative factor, the disease does not occur in other members of the same family.

As regards the sex and race, there appears to be no sexual or racial predilection for the disease. In a study made by periodical examinations of 128 infants weighing 3 lb or less at birth, both the acute and the residual forms of retrolental fibroplasia were found as frequently among male as in female infants, and among Negro as in White infants.

*Aetiology* : The cause of retrolental fibroplasia is yet unknown. No common causative factor has been found in family history, maternal complications during pregnancy or at delivery, or in the neonatal treatment of the infants. Various suggestions have been made from time to time by different writers.

1. Persistence and hyperplasia of the hyaloid system. As already mentioned the original suggestion of Terry (1942) was that it was due to a persistence and overgrowth of the hyaloid system. William Councilman Owens and Ella Uhler Owens (1949) were the first to observe the disease developing in normal eyes in which the hyaloid system had completely atrophied, and their conclusion that the disease is not the result of overgrowth of a persistent tunica vasculosa lentis has since been amply confirmed (Reese and Blodi, 1951).

2. Vitamin E deficiency. This was suggested by Owens and Owens (1949) as a causative factor, and their earlier work appeared to give some encouraging results when vitamin E was given in the early stage. But their claims have not so far been substantiated by others. Thus both Reese and Blodi (1951) and Kinsey and Chisholm (1951) found that vitamin E administration made no significant difference to the incidence of the disease when given from birth or early in the disease. Nor did withdrawing vitamin A and iron (which inhibit the availability of vitamin E) and giving vitamins D and C in water miscible form, have any effect (Kinsey and Chisholm, 1951).

3. Deficiency of adrenocortical hormones. Reese and Blodi (1951) have suggested that the condition is due to a deficiency of the adrenocortical hormones. In support of this theory, they quote high incidence of skin haemangiomas in their cases of retrolental fibroplasia (15 per cent as compared with 3 to 5 per cent in unaffected premature infants). They also quote the results of post-mortem examination of a case of early retrolental fibroplasia, where among other things, there was hypoplasia of the adrenal glands. Following their suggestion, ACTH was widely tried and as in the previous studies on dietary factors, the early reports on ACTH therapy were hopeful. However, when it was used in strictly controlled clinical studies, it was found to have no marked effect on the final outcome of the disease ; instead the use of ACTH was found to be dangerous and has since been abandoned.

4. Oxygen toxicity. Some have suggested that the disease may be related to the way in which oxygen is administered during the early days of infant's life. Both too much and too little oxygen have been suggested as causes, and some have indicated that the disease was related to sudden alteration in the oxygen concentration in the incubators. However, in the light of Ashton's observation, the two conflicting theories as to the role played by oxygen in the pathogenesis of retrolental fibroplasia may be reconciled, the basic injury of vascular obliteration being associated with the initial hyper-oxygenation, while the secondary vascular proliferative phase is associated with the relative anoxia resulting from removal of the infant to normal atmospheric conditions.

5. Infective theory. The variable sporadic and the epidemic-like occurrence of retrolental fibroplasia has led others to suppose that the disease is infectious in nature. Because of the lack of any inflammatory signs in the pathological specimens, this seems unlikely, unless the infectious agent is a virus. As yet, adequate studies have not been made to give an opinion on this theory.

*Pathology* : Friedenwald outlines the histologic changes that are recognised to be characteristic of retrolental fibroplasia. Infants with incomplete retinal vascularisation are



## Retrolental Fibroplasia

susceptible to the disease. The first recognizable histologic lesions are regions of avascularity associated with areas of patchy overgrowth of the retinal capillary endothelium, with the formation of glomerular tufts of varicose capillaries and patchy proliferation of spindle-shaped mesenchymal cells. In later stages, haemorrhages and transudation appear around the abnormal vessels, and the vascular proliferation bursts out of the retina into the vitreous. Retinal detachment results in parts around transudative processes and in part from the fibrosis of the vascular strands in the vitreous. There is little specific characteristic in the cicatricial stage; fibrotic remnants of the so-called glomerular tufts may still be recognizable and may help in establishing the diagnosis.

*Clinical Course* : The National Committee on Retrolental Fibroplasia has divided the clinical course of the disease into two main categories :

1. Acute phase : This stage is sub-divided into five stages as follows :
  - (a) Vascular stage : The retinal vessels become dilated and tortuous. Haemorrhages may or may not be present. Early neo-vascularisation in the extreme periphery of the visible fundus may be present.
  - (b) Retinal stage : In the retinal stage, neo-vascularisation and retinal clouding occur. Haemorrhages are usually present. Vitreous clouding may or may not be present.
  - (c) Stage of slight proliferation : In this stage retina commences to detach and the detachment begins in the periphery of the fundus.
  - (d) Stage of moderate proliferation : Large portion of the retina is detached which may be hemispherical or circumferential.
  - (e) Stage of advanced proliferation : In the late proliferative stage the retina is completely detached and drawn forward to appear as a membrane in the retrolental space.

It should be noted that spontaneous remission is the rule and the progression of the disease may be halted at any of these stages. If the remission occurs before the acute stage has advanced very far, the eye or the eyes may recover without any recognizable damage. On the other hand if the acute stage of the disease has reached an advanced stage before remission takes place, there will develop various degrees of scarring, distortion and destruction.

2. Residual phase : The extent of residual retrolental fibroplasia is classified into five grades as follows :

- (a) Minor changes : Small masses of opaque tissue are found in the periphery of the fundus without visible retinal detachment.
- (b) Disc distortions : Large masses of opaque tissue can be seen in the periphery of the fundus, and from these strands of fibrous tissue stretch towards the disc margin. Thus the disc appears distorted and drawn towards the mass of tissue at the periphery. The side of the disc opposite to the side of attachment of the fibrous strands is often heavily pigmented.
- (c) Retinal fold : One or more retinal folds extend towards the disc from the mass of scar tissue at the periphery.
- (d) Partial retrolental mass : Retrolental mass is seen behind part of the pupillary area. Small areas of attached retina may still be visible or a red reflex may be seen over one sector of the fundus.
- (e) Complete retrolental mass : The retrolental tissue is seen behind the entire pupillary area. In these cases no fundal reflex is present.

*Clinical Features* : When the infant is between the age of 2 and 5 months the parents may seek medical advice for the inability of the baby to face light (photophobia), or for the infant's vision being defective, or for the appearance of a white reflex through the pupil. Depending upon the stage of the disease, the signs will vary and they have already been enumerated. In the terminal stage, there are micro-ophthalmos, shallow anterior chamber, posterior synechiae, corneal opacities, cataract, secondary glaucoma, blindness and searching type of nystagmus.

*Treatment* : There is as yet no satisfactory treatment for this disease. Since the cause is unknown all therapy is still experimental. Irradiation to the posterior pole in the acute phase or surgical removal of the mass in the residual stage has been of no avail. During the acute phase, the pupil should be kept dilated with homatropine to prevent posterior synechiae. If

glaucoma supervenes, miotics should be used. Later on the problem of social adjustment of the child is to be considered.

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## RHEUMATOID ARTHRITIS—See ARTHRITIS, RHEUMATOID

## RHINOSPORIDIOSIS—ITS PREVALENCE IN SOUTH INDIA

C. A. Amesur

Prof. C. Satyanarayana had presented at Washington (1957) a very well received paper on rhinosporidiosis in India under the joint authorship of Amesur<sup>1</sup> and Satyanarayana<sup>2</sup>.

This disease was first recognized by Malbran (Brazil) in 1892 and reported by O'Kinealy (India, Bihar case). Logan Turner-Ashworth (Kerala State case) did the pioneering work in 1924. Cherian reported the first case in a female in 1929, and Amesur<sup>1</sup> first in the maxillary antrum at the fourth International Congress at London in 1949.

Karunaratna (1939) analysed his 104 cases from Ceylon. Cherian and Satyanarayana<sup>4</sup> reported 72 cases in 1948 and Rajam<sup>10</sup> published an admirable paper of a fatal case of systemic disseminations in 1955. More recently isolated cases have been reported from Poland, Turkey<sup>3</sup>, Iran<sup>8</sup> and Mexico<sup>9</sup>.

The life history of the parasite is illustrated in Figure 1 and the histology in Figure 2. The fully formed spore has a chitinous envelope, a vesicular nucleus with a karyosome and cytoplasm in the vacuoles of which lie from 10 to 16 refringent spherules of reserved food matter. The spores are spherical or oval, measuring 7 to 9 $\mu$  in diameter. They are discharged by hundreds through the pore of the sporangium and are scattered throughout the connective tissues. By degrees the refringent spherules of food matter are used up, and the spores enter into fresh connective tissue cells to repeat the cycle. The ripe sporangia are white in colour and 250 $\mu$ -300 $\mu$  in diameter, usually just visible to the naked eye.

**Site of Infection:** The infection in most cases is confined to mucous membranes. The nostrils are the most common site of this infection. This marked predilection for the mucous lining of the nose and nasopharynx is difficult to explain except on the basis of an inherent susceptibility in sandy places. The next site is the ocular apparatus including the eye lid, conjunctiva and lachrymal sac. A few cases have been recorded of the soft palate, uvula, tonsils, pharynx, larynx, trachea and bronchi. Rare cases are seen in maxillary antrum, inferior and middle turbinates and parotid gland. Cherian and Satyanarayana<sup>4</sup> reported a case on the scalp. Rajam<sup>10</sup> (1955) states that penile localisation, first recorded by Ingram<sup>12</sup> is probably more frequent than a few reports in the literature would suggest. Cutaneous localisation of the infection has been very frequently reported by Foresyth on the face, by Allen and Dave on the foot, by Dhayagude<sup>13</sup> on the trunk and extremities. In a fair number of cases multiple growths are seen. In one case in a female, growths were situated in the nose, tonsils, faucial pillars and the uvula. But by far the largest number of growths are seen inside the nose.

The 14 specialists in charge of various big teaching hospitals in the various states of India with a total population of 353,202,532, in personal communications reported 255 cases recorded by them during 1955 which are shown in the table on page 378.

It will thus be noticed that most cases are seen in Malayalam and Tamil speaking areas of Kerala and Madras States of South India. Though the percentage population of these two states is 4.1 and 8.2 they form 51.5 per cent and 19 per cent of the cases seen in 1955. In other words 12.3 per cent of the population gave rise to 69.5 per cent of the rhinosporidiosis cases. These two states have vast shores and sands rich in rare earths (thorium and uranium). Amesur<sup>2</sup> is inclined to believe that the inhalation of these rare earths in the sand may be a causative factor. It is also known that this disease is noticed in Ceylon in people of South Indian origin.

## Rhinosporidiosis—Its Prevalence in South India

Karunaratna<sup>14</sup> points out the tendency for local recurrence of the infection and suggests that the parasite undergoes its complete cycle of development in the human body without the intervention of an intermediate host.

<i>Language spoken</i>	<i>Population Percentage</i>	<i>Cases seen in 1955</i>	<i>Rhinosporidiosis Percentage (in total number of cases seen).</i>
Assamese .. .. .	1.5	0	0
Bengali .. .. .	7.8	12	5.0
Gujerati .. .. .	5.1	0	0
Hindustani .. .. .	46.1	8	3.4
Kannada .. .. .	4.5	29	4.0
Malayalam .. .. .	4.1	123	51.5
Marathi .. .. .	8.2	7	2.8
Oriya .. .. .	4.0	22	9.5
Sindhi .. .. .	0.2	0	0
Tamil .. .. .	8.2	44	19.0
Telugu .. .. .	10.1	7	2.8
Rest .. .. .	0.2	3	2.0
Total population - 353,202,532 .. .. .	100.0	255	100.0

**Mode of Infection :** There is no proof of any contact infection. Experimental inoculations have failed to produce the disease. Amesur believes that rare earths in the sands irritate the nasal mucosa and cause the disease.

**Diagnosis :** Rhinosporidiosis should be suspected in all mulberry polypoidal fleshy growths on the external mucosal surface. If found in an unusual place, a smear should be examined under the microscope for the parasite.

Figures 3, 4 and 5 show cases where naso-pharyngeal, lachrymal and laryngeal areas are affected.

**Treatment :** All medical treatment has so far failed, including pentamidine, as reported by Rajam.

The tumour is removed surgically and the base cauterized with galvano-cautery.

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# PLATE XIII

## RHINOSPORIDIOSIS

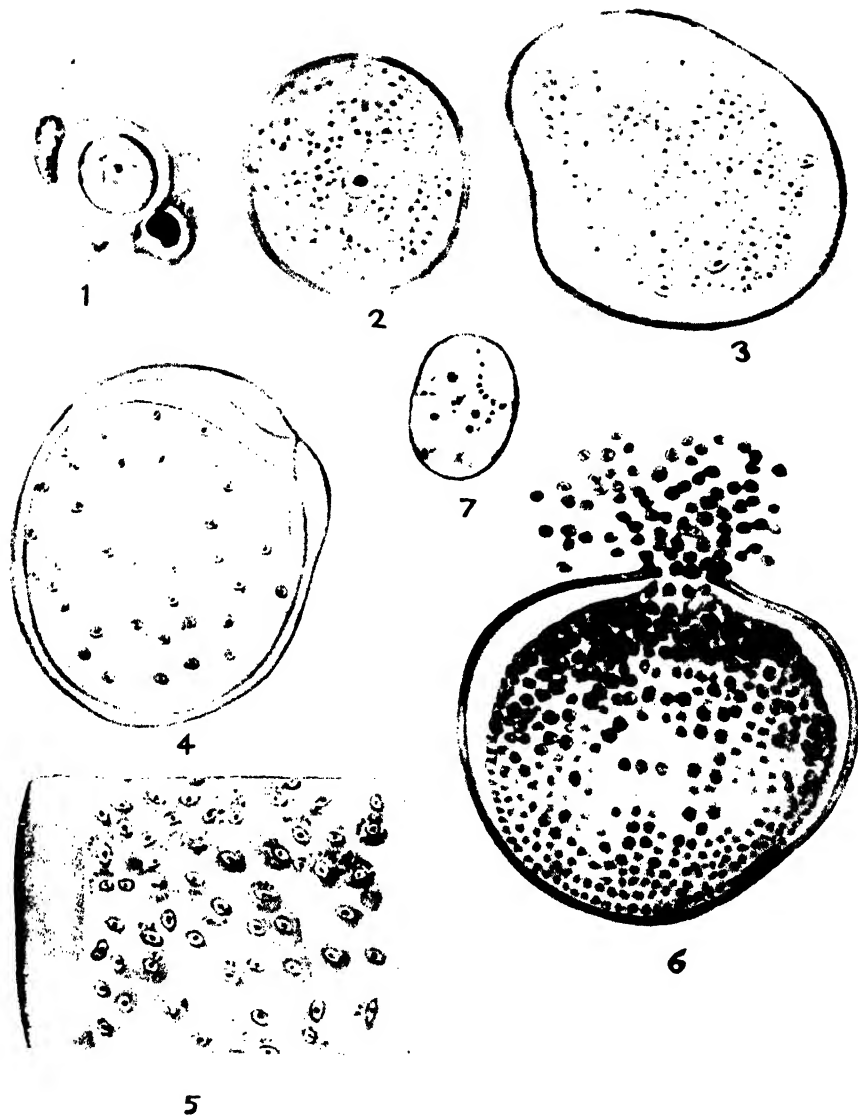


FIG. 1

*Rhinosporidiosis : Morphological characteristics of the various stages.*

1. *Very early stage, between connective tissue cells (60x).*
2. *Later stage with single nucleus (65x).*
3. *Later still with 64 nuclei.*
4. *About 500 nuclei. The envelope consists of chitinous external layer and thick inner cellulose layer.*
5. *Section of contents of the sporangium.*
5. *Discharge of mature spores.*
7. *Section of a spore nucleus with karyosome, cytoplasm with vacuoles and refringent spherules.*

RHINOSPORIDIOSIS



FIG. 2

*Illustrates the histological features of rhinosporidiosis.*



FIG. 3

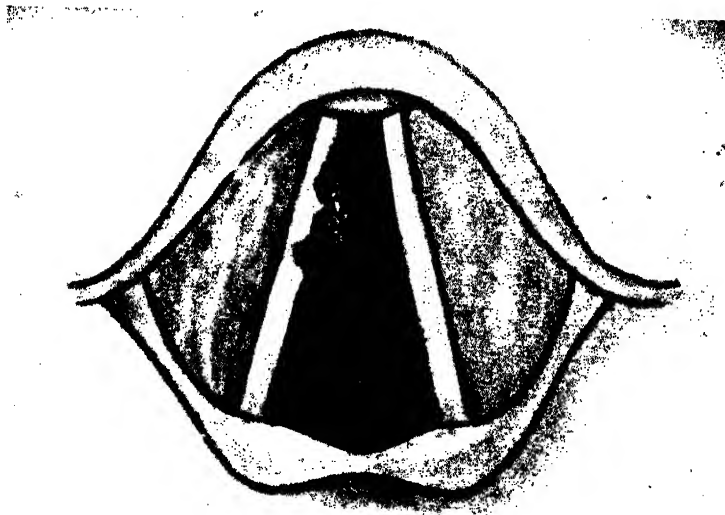
*Rhinosporidiosis of the nasopharynx.*

PLATE XV

RHINOSPORIDIOSIS



FIG. 4  
*Rhinosporidiosis of the lacrimal sac.*





## RICKETS AND AMINOACIDURIA

B. D. Punekar

Rickets is a disease of the blood rather than of the skeletal system. In recent years, this disease has stimulated studies in amino acid metabolism. The present review takes into account studies based on clinical investigations.

The clinical conditions related to the higher excretion of amino acids can be classified into two categories, namely (1) the normal pattern of plasma amino acids with a defective tubular reabsorption (a lower renal threshold) of amino acids from the glomerular filtrate. This defect is limited to different groups of amino acids. Most of the cases of these disorders are hereditary, for instance, in congenital cystinuria. (2) The abnormal concentration of the plasma amino acids arising from the disfunctioning of the metabolic processes. Thus phenylalanine in the cases of phenyl-pyruvic-oligophrenia can be cited as an example.

The aminoaciduria associated with rickets belongs to the first category and it can be explained on the basis of the failure of renal reabsorption. In the Toni-Fanconi-Debré syndrome, rickets is accompanied by aminoaciduria. There is also renal glycosuria and phosphaturia with vitamin D-resistant rickets or osteomalacia. A number of other conditions which give rise to aminoaciduria may also be stated. Vitamin C or vitamin E deficiency and poisoning by lead and uranium increase the level of amino acids in the blood. Certain liver diseases result in a higher concentration of amino acids, both in the blood and the urine.

The clinical condition associated with the Toni-Fanconi syndrome has two clear cut types of pictures; the juvenile type and the adult type. According to Bickel and Harris (1952),<sup>1</sup> who have distinguished these two varieties, both are a result of a recessive hereditary factor. In the juvenile type, Bickel et al (1952)<sup>2</sup> have observed a deposition of cystine crystals in the reticulo-endothelial system, particularly in the Kupffer cells of the liver, in the spleen, the bone marrow, the lymph glands and in the histiocytes of the connective tissues; it proves fatal in many cases. Milne et al (1952)<sup>3</sup> and Stowers and Dent (1947)<sup>4</sup> have studied a very rare adult type, in which they find no complications of cystinosis. This indicates that the amino acids which are reabsorbed as phosphate esters are lost, resulting in severe osteomalacia. The reabsorption of phosphate is defective in rickets and it is, therefore, natural to attribute the aminoaciduria to a failure of the tubules to reabsorb the amino acids. Stowers and Dent (1947)<sup>4</sup> have claimed that the plasma amino acids in the adult are in normal concentration, whereas in the juvenile type Bickel et al (1952)<sup>2</sup> have found that the various amino acids are in an increased concentration. This has been proved by both chromatography and by microbiological assay. However, in many respects the renal defects of the two types show a considerable similarity and hence there may be a tendency to acidosis and also increased excretion of ketone bodies in both.

In the light of the general role of protein and essential amino acids in human nutrition, it is apparent that the aminoaciduria may contribute to malnutrition. Jonix and Huisman (1953, 1954)<sup>5,6</sup> have reported that vitamin C or D deficiencies in infants and children show a higher urinary excretion of amino acids. The unusually large quantities of amino acid excretion in rickets consist of both the free and the bound form of amino acids, namely, lysine, histidine, glutamic acid, glycine plus alanine and threonine plus serine. Jonix and Huisman (1953)<sup>5</sup> have also noted that the rate of amino acid excretion falls slowly after the administration of vitamin D but does not reach a steady level until after three or more weeks. In some of the patients the rate of excretion of amino acids never comes to normal and the adults, who had rickets in childhood, continue to have some aminoaciduria. Harrison (1954)<sup>7</sup>, on the other hand, has found a complete return to normal level of amino acid excretion after treatment of rickets with vitamin D.

The renal element plays a very important role in aminoaciduria of rickets as proved by Jonix and Huisman (1954)<sup>8</sup>. They determined the level of different amino acids in the plasma ultrafiltrate of normal and rachitic children, separately. Again, they raised the level of certain amino acids in the plasma in both the cases, namely, normal and rachitic children and studied the amount of amino acids subsequently excreted. The levels of histidine and arginine in the plasma, before and during the intravenous administration of the amino acids, were not higher in rachitic than in normal children. The rachitic children receiving histidine and arginine intravenously showed (1) a higher excretion of histidine, five to ten times more than the control, whereas, (2) little change was observed in the urinary concentration of arginine. The intravenous administration of histidine and arginine is also found to cause a slight increase in the excretion of threonine, serine, glycine and lysine and sometimes tyrosine, in children suffering from rickets.



## Rickets and Aminoaciduria

Vitamin D helps the proper re-absorption of histidine and arginine. Similar findings were reported by Fisherman<sup>9</sup> (1955) with the administration of methionine to cause a greater increase of urinary amino acids in vitamin D-resistant rickets. It is, therefore, apparent that rachitic children, who excrete large amounts of certain amino acids in their urine, have normal levels of these amino acids in their plasma.

Huisman (1954)<sup>10</sup>, using the chromatographic analysis with Dowex 50, has determined the ninhydrin positive substances of plasma filtrates, before and after hydrolysis. He showed that in the case of two normal adults, four normal children of different ages, two children with scurvy and three patients with some form of rickets most of the common amino acids are present in the plasma filtrates in notable amounts while only hydroxyproline is lacking. Aspartic acid and glutamic acid are present in large amounts as asparagine and glutamine, while after hydrolysis only alanine, valine, leucine, phenylalanine, histidine and perhaps threonine and serine have increased in concentration.

Jonix (1955)<sup>11</sup> has noted that the higher amount of urinary excretion of amino acids in the other members of a rachitic family, even though they showed signs of healed rickets, suggests the existence of a hereditary factor, which at the same time influences the excretion of the amino acids. The administration of vitamin D in the various types of rickets did not succeed in bringing the urinary amino acid excretion to normal in a short period. The degree of amino acid excretion varied according to the severity of rickets.

Rickets can be healed by citric acid or sodium citrate. Jonix (1955)<sup>11</sup> has carried out investigations with the administration of neutral sodium citrate on the urinary amino acid excretion of rachitic children. He observed no healing in his X-ray studies nor any change of phosphate level in the blood. The serum calcium decreased slightly whereas the phosphate level of urine distinctly decreased, perhaps due to a higher retention of phosphate in the body. Vitamin D is supposed to help in the proper utilization and absorption of calcium and phosphorus, which when administered to the same rachitic children, bring down the higher urinary amino acid level to normal. Citrate does not seem to have any influence on aminoaciduria. It is, therefore, conceivable that citrate is unable to give a protective influence to the amino acid set up of the body in rachitic children, whereas vitamin D does achieve this to some extent.

In the light of relevant literature a question that would naturally arise is whether the diminished re-absorption of the amino acids in rachitic children due to the failure of kidney tubules, which in its turn is caused by vitamin D deficiency or, is it due to the activity of the parathyroid glands on the re-absorption by the kidney tubules? It is already known that the parathyroid has a stimulating action on the absorption of phosphorus by the kidney tubules. If so, why does the parathyroid not help in the absorption of amino acids? The investigations of Weaver and Neill (1954)<sup>12</sup> have shown aminoaciduria in patients with pernicious anaemia. Punekar (1958)<sup>13</sup> on the basis of his animal experiments suggests that vitamin B<sub>12</sub> administration diminishes the urinary excretion of amino acids bringing it to normal. It, therefore, indicates a close similarity between vitamin D and vitamin B<sub>12</sub>. In both these deficiencies the majority of the changes seem to take place in the bones. The deficiencies are again reflected in the blood and further cast their picture in the urine resulting in aminoaciduria. If it is taken for granted that renal failure is not the main factor for aminoaciduria in rachitic conditions, the nutritional deficiency may be responsible for the amino acid disorders of the body. All these questions are vague and so far unsolved, and may be explained on the basis that the trace amounts of vitamin C, vitamin D or vitamin B<sub>12</sub> help in some way in correcting the nutritional deficiency by enhancing the utilization of circulating amino acids of the blood for building the fixed tissues of the body and thereby causing a diminished urinary excretion of amino acids.

The observations of the urinary amino acid concentration of two hyperthyroid patients studied by Jonix (1955)<sup>11</sup> do not prove aminoaciduria, but a considerable urinary increase in the level of phosphate, which establishes that hyperthyroidism is not the cause of aminoaciduria in rickets.

Jonix and Huisman (1954),<sup>8</sup> Jonix (1955)<sup>11</sup> and Huisman (1954)<sup>14</sup> have suggested a probable cause for the failure of re-absorption of amino acids which are normally considered to be absorbed as phosphate esters by kidney tubules. The same workers have also observed a similar disorder in scurvy. It is, therefore, more likely, that vitamin D, vitamin C and vitamin B<sub>12</sub> are essential for the normal functioning of some enzyme system, which helps in the re-absorption of amino acids in the tubules. The nutritional deficiency in one of these vitamins impairs the enzymatic

## Rickets and Dental Caries, Calcium Fluoride as Prophylactic in

system and causes aminoaciduria. A relation between vitamin D activity and a hereditary factor can also be based on the enzymatic disorders, which lead to the hereditary variation according to the functioning of the enzymes.

### SUMMARY

Aminoaciduria in rickets is due to a failure of the renal tubular re-absorption of amino acids and is a result of a recessive hereditary factor. The abnormal increase in the urinary excretion of amino acids consists of both the free and bound forms of amino acids, namely lysine, histidine, glutamic acid, glycine plus alanine and, threonine plus serine. The administration of vitamin D diminishes the urinary amino acid excretion but the plasma amino acid concentration remains the same before and during the administration of vitamin D.

The re-absorption of phosphorus by the renal tubules seems to be under the influence of parathyroid, but no direct relationship can be established between phosphorus and amino acid re-absorption by the tubules. Citrate does not seem to offer any protective action in preventing aminoaciduria in rachitic disease nor can hyperthyroidism be taken as a cause of aminoaciduria.

Some type of enzyme system is predicted for the re-absorption of amino acids, and vitamin D, vitamin C and vitamin B<sub>12</sub> are considered to be essential for the proper functioning of these enzymes.

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## RICKETS AND DENTAL CARIES, CALCIUM FLUORIDE AS PROPHYLACTIC IN

J. B. Mehta

Large numbers of studies have confirmed the fact that fluorine has a definitely beneficial effect on the tooth enamel and the prevention of dental caries<sup>3</sup>. To this effect the best way to provide fluorine to the population is through fluoridation of the water supply. Fear of chronic fluorosis arising out of this has ever been present. However, the Medical Research Council of the U. K. reported to the Ministry of Health that there was no definite proof that fluoridation of water to the extent of 1 part in a million was harmful<sup>1</sup>.

Calcium as a prophylactic against rickets is also well-known. Therefore the question naturally arises whether fluoridation of water with calcium fluoride rather than with sodium fluoride may not be doubly beneficial. Calcium salts are less freely soluble. While only 37 to 54 per cent of fluoride as bone meal and 65 per cent of calcium fluoride in the solid form are absorbed from the intestine, between 82 to 97 per cent sodium fluoride in solution is absorbed from the intestine<sup>3</sup>. Large amounts of calcium in the diet of rats depressed fluoride absorption. Gebauer carried out a series of experiments on rats. (1) Feeding of sodium fluoride to rats maintained on a rachitogenic diet did not prevent rickets. (2) Fluorine given to rats already suffering from rickets had no therapeutic effect. (3) He fed calcium fluoride to rats on a rachitogenic diet and a control group that had calcium carbonate in place of calcium fluoride. Rickets seemed to be precipitated by calcium fluoride as a source of extra calcium. These experiments on rats are not very encouraging for combining prophylaxis of dental caries and rickets by supplying calcium fluoride in the diet or water supply<sup>2</sup>.

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## SARCOIDOSIS

D. Jaganatha Reddy

Sarcoidosis is the subject of innumerable articles and several monographs. The most instructive and recent of these is the review and report of investigations of 160 cases including 30 necropsies, by Longcope and Freiman. The disease is characterised by the presence of circumscribed discrete masses, either visible or only disclosed at routine histological examination of tissues. The lesions although bear a similarity to tuberculosis are yet distinct on account of absence of caseation, necrosis and tubercle bacilli. Hyalinosis and fibrosis are often observed as the age of the lesion advances. Asteroid, Schaumann, and nonlipoid crystal giant cell inclusion bodies are often reported although they are not specific for the lesions. The aetiology is still unknown.

Reports of sarcoidosis from this country are very few. Authentic necropsy reports of two cases of sarcoidosis were recorded by Reddy for the first time in 1954. They were incidental autopsy findings in medicolegal cases of deaths. In one of them the typical lesions of sarcoidosis were seen in the liver, spleen and lungs (Figs. 1, 2, and 3). In the lung the lesions were perivascular and appeared to be in the early stage of formation, while those in the spleen and liver were well-formed and circumscribed. There was absence of caseation and of tubercle bacilli and in addition, the lesions were marked by intact reticulum network (Fig. 4). Giant cell inclusion bodies were spotted in lesions of the spleen (Fig. 5). No cause for sarcoidosis was recognised in both the cases but the author suggested to look for allergic helminthic reaction in such cases.

Chatterjee and Ghosh reported sarcoidosis of cervical and paratracheal lymph nodes confirmed by biopsy examination and failure to spot acid-fast bacilli in a girl aged 14 years. Tuberculin test was positive 1 in 10,000 and excellent response to antituberculous drugs was noticed. This again makes both the pathologist and the clinician sceptical about the narrow and uncertain margin of distinction between tuberculosis and sarcoidosis.

Most informative and illuminating review on sarcoidosis from India in recent years is that of Rajam et al. These authors recorded sarcoid lesions in a middle-aged woman, in the skin, lymph nodes, lungs and bones. Sarcoidosis was reported on examination of the biopsy material of one of the many cutaneous nodules. The bilateral hilar skiagraphic shadows and the marked asymptomatic enlargement of the cervical lymph nodes roused their suspicion of sarcoidosis. This was confirmed by a negative tuberculin test, positive Kveim's reaction, hypercalcaemia, hyperglobulinaemia, and pathognomonic and typical circumscribed and non-caseating granulomatous lesions with giant cell inclusion bodies in sections of the lymph nodes studied. Regression of the skin nodules, lymph nodes and the hilar shadows was noticed on prednisolone therapy. Serial skiagrams of chest taken at varying intervals during treatment showed remarkable clearance of the bilateral hilar opacities.

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## SCHISTOSOMIASIS, RELATIONSHIP TO POLYPOSIS AND ADENOCARCINOMA OF COLON—See COLON, POLYPOSIS AND ADENOCARCINOMA OF, RELATIONSHIP TO SCHISTOSOMIASIS

## SCHIZOPHRENIA

N. S. Vahia

Interest in this illness is so great that the last International Congress for Psychiatry at Zurich was almost exclusively devoted to the discussion on schizophrenia. It was attended by more than a thousand psychiatrists from all over the world. The nature of this illness was discussed from various points of view.

Relationship between the experimentally produced psychosis and schizophrenia is not established, but it is interesting to note that it is possible to produce psychotic reactions of schizophrenic type with the help of drugs like lysergic acid diethylamide (LSD 25)<sup>1, 20</sup>. Whether the relationship between this state and schizophrenia is only superficial or whether schizophrenia is probably due to an unknown toxin is at present a matter of opinion.

PLATE XVI

SARCOIDOSIS

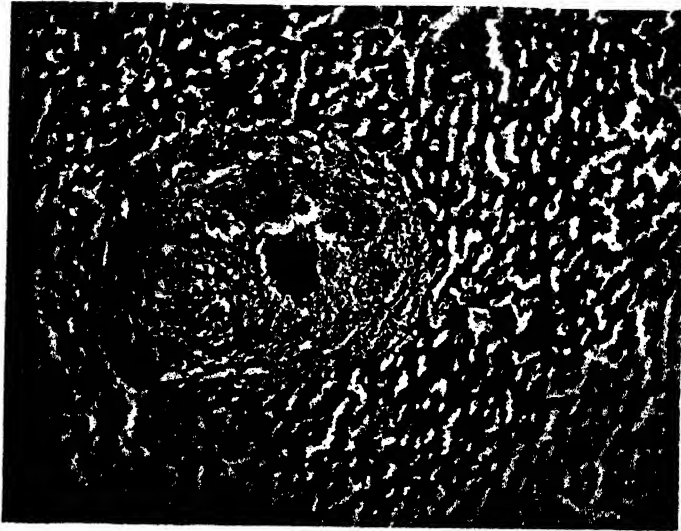


FIG. 1

*Sarcoidosis of the liver*

*Illustrates circumscribed sarcoid lesion in the liver. No caseation is seen. Multiple giant cells are seen (H&E X60).*

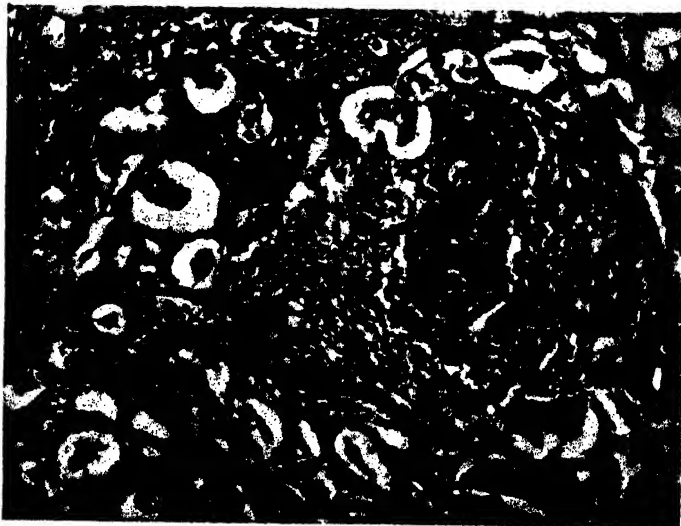


FIG. 2

*Sarcoidosis of the lung*

*Illustrates early sarcoid lesion in the lung. The epithelioid cell collections are seen around vessels (H&E X60).*

PLATE XVII  
SARCOIDOSIS

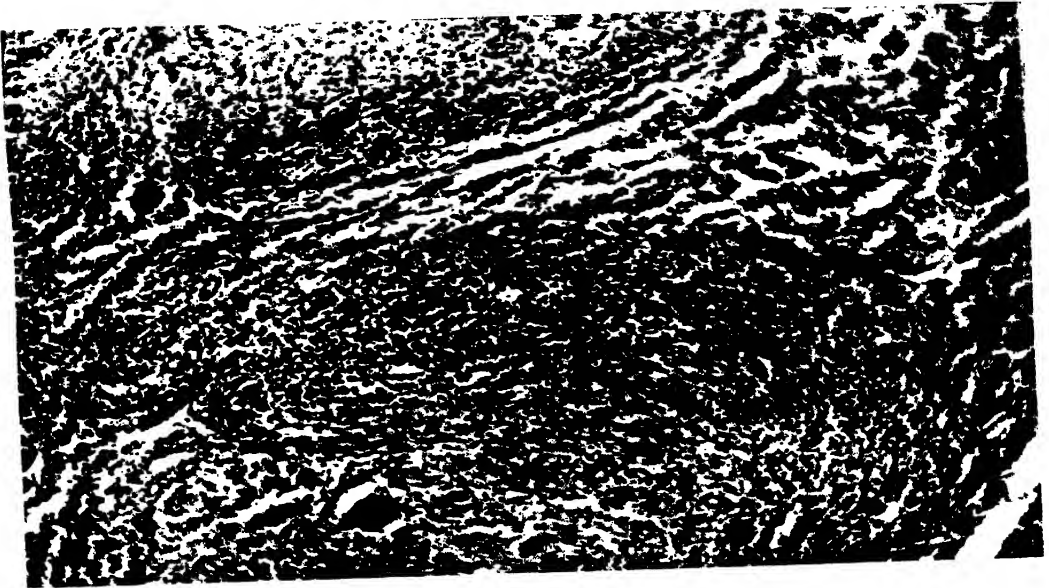


FIG. 3  
*Sarcoidosis of the spleen*  
*Illustrates multiple circumscribed sarcoid lesions with giant cells*  
*(H&E, X60).*

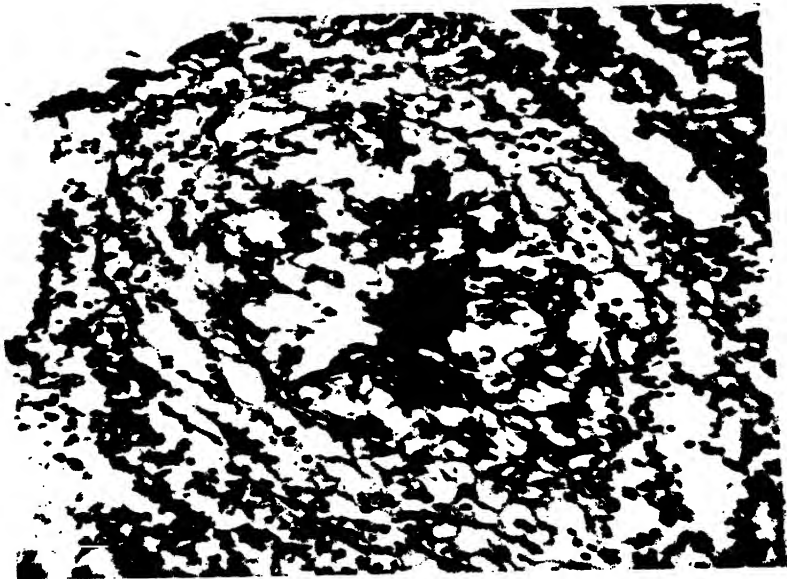


FIG. 4  
*Sarcoidosis of the liver*  
*Illustrates intact reticulum in a sarcoid of the liver*  
*(Foot Stain, X60).*

*PLATE XVIII*

**SARCOIDOSIS**



**FIG. 5**

*Sarcoidosis of the spleen*

*Illustrates inclusion body in giant cell in the sarcoid lesion of the spleen (H&E x840).*



Heath et al<sup>8</sup> injected a protein substance from the serum of schizophrenic patients in 20 human volunteers. Controls were kept and a double blind technique was used. All the patients receiving the protein developed symptoms of schizophrenia, the controls remained symptom-free. They had an impression that the nature of the presenting symptoms depended upon the dosage rather than the personality traits of the recipients or the donors. This interesting work is being continued from different aspects.

Malis<sup>15</sup>, who studied the biological properties of the blood of schizophrenic patients from influence on plant growth, activity of the perfused heart etc. has revealed the presence of certain toxic substances in 51 per cent of such cases. These substances were neither hormones, nor products of metabolism, nor were they derived from the autonomic nervous system. In view of these and other considerations the author postulated that the disorder of the brain in schizophrenia was caused by toxic substances derived from other organs, probably infected by virus. He then studied the immunological properties of blood and other body fluids by means of A.V.B. reaction (agglutination of virus-laden bacteria). Altogether 155 patients were studied, 90 with schizophrenia of some years' duration and 65 controls. A specific antigen was found in the blood of 51 per cent of schizophrenics. The control group gave either negative or very mildly positive agglutination reaction.

Studies of the functions of the adrenal cortex, pituitary, thyroid and liver, have not led to any significant correlation between their functions and schizophrenic illness<sup>3,4,19,22</sup>. Similarly studies on glutamic acid metabolism, carbohydrate metabolism, blood copper and aromatic excretory patterns in schizophrenia have not helped in understanding the disease<sup>2,4,6,9,10,17</sup>.

Those who believe in psychological factors as being the most important causative factors, have studied the early environment of the schizophrenic patients and the fathers and mothers of these patients. Kohn et al<sup>13</sup> have described mothers of schizophrenic patients as domineering and over-protective and not allowing the satisfactory emotional development of a growing child. Lidz et al<sup>14</sup> described three categories of fathers of schizophrenic patients: (1) Fathers of schizophrenic daughters constantly in battle with their wives with whom they are dissatisfied and struggling to make their daughters to follow their pattern; (2) fathers, who cannot endure the rivalry of a son for the wife's attention, (3) passive fathers. These findings might be suggestive, but not of primary importance in the aetiology of schizophrenia.

Kallmann<sup>11</sup> has shown that adult schizophrenia appears to have a direct correlation with heredity. More recently he studied genetic aspects of pre-adolescent schizophrenia<sup>12</sup>. He compared the family background of 52 twins and 52 singletons with those of comparable adult sample. The findings indicated an early effect in childhood schizophrenia of the same genotype assumed to be responsible for adult schizophrenia.

Parfitt<sup>18</sup> has advanced a hypothesis that schizophrenia is an expression of an inborn defect in certain parts of the brain, a progressive disease that produces at first disorder and then inactivity in brain function, beginning from frontal, temporal or hypothalamic region. This inborn error produces ontogenetically inevitable pathology or pathology made to manifest by factors not recognised at present to be pathogenic. The disease then spreads with or without periodic recession and it may even become arrested. In short, he suggested that "schizophrenia is a kind of phylogenetically and ontogenetically determined encephalopathy".

Jung<sup>10</sup> has suggested that probably schizophrenia is primarily psychogenic with probably secondary toxic effect, at least in mild and latent cases that were treated by him in his practice.

**Classification:** There is a great difference of opinion regarding the classification of schizophrenia. The original classification of Krepelin is not acceptable to many, but so far no other classification has been generally accepted. Pseudoneurotic form of schizophrenia has been fairly well accepted. Fish<sup>7</sup> has presented another classification.

**Treatment:** As long as the aetiology of schizophrenia remains obscure, any treatment is bound to be empirical.

Tranquillizers are in vogue in the control of acute schizophrenic reaction. They are also of use in decreasing psychomotor excitement in chronic cases. Modified psychoanalytical psychotherapy is advocated by Rosen<sup>21</sup>, Bychowski<sup>5</sup> and others. Insulin coma treatment is still being used extensively. Electrical convulsive treatment, according to some workers is also as efficacious as insulin coma treatment. Leucotomy is considered to be useful in early stages if



## Seizures

other treatments fail. When indicated, transorbital leucotomy or bimedial leucotomy is more advisable than standard leucotomy, because of decreased chances of personality changes. (Details regarding the place of tranquilizers, insulin coma treatment, electrical convulsive treatment and leucotomy have been discussed elsewhere in this book.)

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## SECTIONAL RADIOGRAPHY OF THE CHEST—See RADIOGRAPHY OF THE CHEST, SECTIONAL

## SEIZURES

G. V. Satyanarayanamurthi

The term "seizures" must be deemed a generic term which includes all types of abnormal discharge of activity from the brain and embraces both surgical and medical conditions inclusive of idiopathic epilepsy<sup>21</sup>.

**Historical:** In the current text-books on the history of medicine, no attention is drawn to ancient Indian medical lore. Though it cannot be said that ancient Indian medical men had clear conceptions of idiopathic epilepsy as a clinical entity, there are certain terms such as 'dhantha sthanithathavam' (chattering of teeth), 'mookathvam' (loss of consciousness), 'asabda sravanam' (auditory hallucinations) and 'manaschanchala' (abnormal behaviour) occurring in Charaka<sup>21</sup>.

Records in history show that idiopathic epilepsy is not incompatible with high intellectual accomplishments<sup>19</sup>. Alexander, Julius Caesar, Byron etc, were known to be afflicted with this disease. It is deemed that epileptic brain is an irritated brain and is capable of great effort and need not necessarily go with mental deficiency, which incidentally is a very rare complication of idiopathic epilepsy and may be accidental.

**Occurrence:** During the 5-year period from 1952-1957, there have been only 250 cases of idiopathic epilepsy in the author's clinic and computed at that rate, 1 in 700 for the hospital

population and should indeed be much less against the total population, due to factors which require very careful investigation.

*Aetiology and Pathology:* To speak of a 'seizure threshold' in the causation of seizures is a useful concept in the understanding of seizures. The seizure threshold is very low in infants and hence the frequency of convulsions in children. The threshold is influenced by hereditary factors, disease and degeneration of the nervous system, and emotional and psychological factors. In fact, marriage laws tabooing intermarriage among those afflicted with seizures were instituted quite early. William Lennox contends that 84 per cent of both of identical twins manifested seizures (Caveness<sup>6</sup>).

Wilfred Nev<sup>18</sup> investigating a group of 272 cases of idiopathic epilepsy found arachnoidal fistulae through which cerebrospinal fluid leaked into the subdural spaces in practically every epileptic patient who presented no other defect. He contends that any factor which causes the escape of cerebrospinal fluid of the brain or which causes tears in the fine strands of tissue, at once abolishes the normal stability of the brain and makes it irritable. This contention is not confirmed by others.

Gilbert Philips<sup>8</sup> studied the clinical histories of 2000 cases of closed head injuries in the Head Injury Bureau at Oxford and found that post-traumatic epilepsy occurred in 6 per cent of unselected cases. Cases with a long post-traumatic amnesia had a higher incidence of epilepsy.

Alfred Meyer et al<sup>1</sup> investigating cases of temporal lobe epilepsy, pointed out that incuscular sclerosis due to birth mechanisms cannot be the only aetiological factor and that other events, particularly infections and new growths occurring in infancy, childhood and early adolescence, play an important part in the causation of this condition. Tumours, cirroid aneurysms, porencephalic cysts and scars of penetrating injuries have been found in these cases. But in some cases however no demonstrable lesion can be made out clinically, on pathological examination, or by angiography.

Weller and Norman<sup>20</sup> reported the occurrence of a case of idiopathic epilepsy due to birth injury in one of the twins giving rise to mental retardation and epilepsy and the child dying in status epilepticus while the identical twin was normal. They contend that epilepsy can occur due to birth injury without a genetic predisposition.

Northcroft and Wyke<sup>17</sup> studying 100 consecutive cases of intracranial abscess found that half of the surviving patients developed seizures within 6 months to a year after completion of surgical treatment. They contend that these should be electroencephalographically investigated and if necessary the cicatrix should be excised.

Helen Dimsdale<sup>10</sup> investigated 200 cases of idiopathic epilepsy starting after the age of 20 years excluding traumatic cases and those with papilloedema and found abnormalities in 37 per cent of cases under the age of 40 years and in 63 per cent in those above that age group. Above 40 years, tumours were more frequent while in the 3rd and 4th decades angiomas were the commonest cause. Complete neurological investigation and electroencephalography should be combined with pneumo-encephalography. Angiography is particularly useful in detecting angiomas.

Liddell and Retterstol<sup>14</sup> report that chlorpromazine administered alone could cause seizures in mental cases for whom prefrontal leucotomy was done. They advocate that antiepileptic treatment should be combined with chlorpromazine therapy in such cases.

Meyer et al<sup>15</sup> noticed unusually severe vascular damage in a case following status epilepticus. Subsequently the patient had grand mal, petit mal and also temporal lobe seizures. When he died 12 months later, there was widespread damage to that part of the brain termed "visceral brain" due to circulatory and anoxic disturbance. They discuss the pathogenesis and functional significance of the lesions.

Tonniss and Mackenzie<sup>12</sup> have shown that focal epilepsy and episodic headache may occur as cardinal clinical features of a cerebral angioma which should be investigated by angiography and radical treatment done if there is evidence of it.

John Laidlaw<sup>11</sup> and Barbara Ansell and Edwin Clarke<sup>4</sup> investigating catamenial epilepsy, claim on statistical evidence that there is a reduction of fits during the luteal phase with an increase immediately before, during and after menstruation. They contend that the catamenial periodicity may be due to an anticonvulsant action of progesterone with an exacerbation of fits when its secretion stops.

## Seizures

*Classification of Epilepsy*<sup>13</sup>: In the past decade epilepsies have been classified on the electroencephalographic findings which supplanted the clinical classification of grand mal and petit mal. The problem was reviewed by Clerk and Knott who found that this is not consistently valid. The logical development in the classification of epilepsy is to group them according to the site of origin of the epileptic discharge. This was envisaged by Hughlings Jackson in his conception of aura, or "local sign" of an attack as demonstrating its site of origin. Electroencephalographic investigations would appear to have amply justified this contention. Present evidence suggests that the initial disturbance in petit mal may be in the thalamus; we may very soon be able to recognise with some confidence cortical, thalamic and even hypothalamic epilepsies. This may probably be modified with the increasing knowledge of the complexity and profusion of connections between cortical and subcortical structures.

Allan A. Bailey<sup>2</sup> draws attention that in idiopathic epilepsy, a variety of phenomena which may not produce any loss of consciousness, amnesia, or anything that can be called a convulsion can occur in episodes of short duration lasting much less than 15 minutes and rarely lasting several hours. The attacks may come in clusters of 2 or 3 in one day, and then none may appear for weeks or months. The complaints may be so bizarre as to suggest that the symptoms are a neurotic or psychotic reaction.

David Dalay<sup>6</sup> states that the seizures in idiopathic epilepsy originate in this highly specialised region and produce ill-formed caricatures of the normal activity of the affected region. Donald W. Mulder et al.<sup>7</sup> have shown that paroxysmal psychiatric symptoms consisting of forced thinking, hallucinations, illusions, disturbances of mood and automatism can occur as manifestations of seizures.

Dalay analysing 95 records of patients showed that seizures in 21 patients were secondary to tumours of temporal lobe, in 21 due to atrophic lesions of the temporal lobe and in 53 without any obvious pathology but with abnormal electric foci in the cerebrum.

Hadow M. Keith<sup>9</sup> draws attention to the misuse of the term petit mal. He suggests that the minor seizures may be divided into (a) simple petit mal seizures, (b) akinetic seizures, (c) the abortive convulsion or minor motor seizures and (d) other types of seizures such as involuntary jerking of groups of muscles without loss of consciousness and (e) the 'psychic equivalent' or 'automatism'.

The simple petit mal seizures are rather common among children. They occur several times in the day and according to Jasper and Droogleever-Fortuyn's experimental investigation, the characteristic spike and wave E. E. G. pattern of petit mal could be reproduced in cats by rhythmic stimulation by brief shocks to a small area about 2 mm square in the medial intralaminar region of the thalamus.

Max Levin<sup>16</sup> investigated the diurnal rhythm in epilepsy and attributes it to the unduly unstable state of the brain in the early hours of the morning when the brain has recuperated after sleep. He is unable to explain the nocturnal fits that occasionally occur when the patient has gone to sleep and the brain has not yet recuperated.

*Treatment*: Allan A. Bailey<sup>2</sup> emphasized that treatment of epileptic seizures is a major undertaking and consists of a careful investigation and diagnosis to exclude organic diseases of the brain, particularly tumours of the brain.

Status epilepticus is a medical emergency and the aim of treatment should be rapid and safe control of seizures regardless of their cause, while investigation and diagnosis will have to go on concurrently. The usual mistake is to give too little of an anticonvulsant and to rely too soon after some recovery on oral administration of drugs. Sodium amytal should be given intravenously with the usual precautions attendant upon giving anaesthetic agents. The initial dose varies from 4 to 15 grains given intravenously in 24 hours followed by luminal sodium 2 to 4 grains intramuscularly every 4 to 6 hours and continued for 2 days after oral medication is started.

All minor seizures are not petit mal. Seizures which are strictly of petit mal type are relatively unaffected by barbiturates. Tridione and the closely related drugs are the most effective.

Side effects will have to be watched. Phenurone is another drug and is useful for petit mal as well as grand mal and it also causes undesirable side effects.

Ketogenic diet is recommended but it is not practicable.

Treatment of grand mal seizures of idiopathic epilepsy consists in the use of various sedatives and anticonvulsant drugs that are available. Treatment should be continued for a period till the

patient is free from fits at least for two years, and should not be stopped during the changing periods of life such as adolescence and menopause. Drugs must be chosen carefully and for their specificity of action.

Environmental tension is important and requires careful investigation and advice. Precipitating factors such as sensory stimuli, hearing of music or seeing flickering lights have to be avoided. Alcoholic beverages are contraindicated. Each patient is a problem by himself and has to be given individual consideration.

Indian literature on seizures is singularly scant and is possibly due to lack of modern facilities in the investigation of such cases.

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#### SERODIAGNOSIS OF SYPHILIS—See SYPHILIS, SERODIAGNOSIS OF

#### SEX, DETERMINATION OF

K. Bhasker Rao

Male or female ? The basic genetic difference lies in the sex chromosomes, XX (female) and XY (male)—the Y chromosome being smaller. Barr and Bertram (1949) were the first to discover a small chromatin mass (nucleolar satellite) in the cells of the female. This mass, now called sex chromatin, is seen in 50 per cent of nuclei of the basal cells in the skin of human female—as a dense plano-convex or triangular mass with its apex against the nuclear basement membrane. This is seen in under 5 per cent of males, and in most cases it is difficult to identify from artefacts. This sex chromatin has also been identified in circulating polymorphs as drumstick-like projections from some of the nuclei. It is formed by the fusion of sex chromosomes XX when the cells are in the resting phase and not during mitosis (Shettles)<sup>1</sup>. Shettles and also Dewhurst<sup>2</sup> have attempted to predict the sex of the child before its birth by a study of the cells obtained by centrifugalisation of the liquor amnii. The liquor amnii is obtained by paracentesis of the uterus at about 36 weeks of pregnancy though antenatal sex typing can be done soon after the formation of the liquor. Shettles has given in detail the method of preparation of the smears and the staining techniques. Both authors found that the cells obtained by this type of aspiration biopsy, were not only from the skin but also were from the genitourinary, gastro-intestinal and respiratory tracts. Smears from each of these sources in the female showed the sex chromatin body in about 28-65 per cent of the nuclei. In no

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case of the male did the nuclei show the sex chromatin mass (Shettles). Correct prediction of the sex of the child was done by both workers in all the cases studied.

Apart from histologic studies, biochemical tests based on sex hormones in the saliva were made by colorimetric estimations by Ellin et al<sup>3</sup> and in 81 per cent accurate sex prediction was given. This method is therefore not as accurate as the method previously described, though it is less hazardous than paracentesis.

But this method of sex determination has been utilised for verifying the sex in pseudohermaphroditism. By skin biopsy the genetic sex and the gonadal sex can easily be determined—because both will be identical and it is unnecessary to subject these patients to elaborate endocrinologic tests or to a laparotomy to find out the correct sex. This method is again helpful in cases of gonadal agenesis in the female; and in the male, when teratomas are seen, this method of sexing can be used to determine whether it is a neoplasm or actually “a twin”<sup>4</sup>.

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## SEX DIFFERENCE IN NEUTROPHILS

V. C. Anguli

In 1954, Davidson and Smith demonstrated a sex difference in the nuclear structure of the human polymorphonuclear leucocytes. In routine differential smears of peripheral blood stained by the Giemsa technic they found in the female, a characteristic drumstick consisting of a solitary chromatin mass attached to one of the main lobes of the nucleus by a fine chromatin thread. The chromatin mass, a sharply delineated, round, solid, homogeneous structure approximately 1.5 microns in diameter, was readily visible at a magnification of 90. The simplicity of this method for the determination of genetic sex, as compared with skin biopsy advocated earlier by Barr and his associates led Tenczar and Streitmatter to undertake the following study in an attempt to confirm the findings of Davidson and Smith.

*Method:* Routine blood films stained by Wright's method were collected from 100 adults by a technician who recorded the sex of the patient. In no instance was the sex of the patient known to the authors until after examination of the blood smear.

Characteristic female nuclear chromatin appendages are usually found in mature lobulated neutrophils and are rare in stab forms. They are readily identified by the criteria of Davidson and Smith noted above. They observed characteristic female nuclear appendages in 3 eosinophils; none were encountered in basophils. Minor lobes, small clubs, sessile nodules, tags, and racquet bodies must be distinguished.

*Discussion :* In 1949 Barr and Bertram demonstrated a sex difference in the intermitotic nuclear structure of neurons from the central nervous system of male and female cats. Subsequently, Barr and his associates extended this observation to many other species including man and showed that a similar nuclear sex difference was readily apparent in most somatic tissues. Moore, Graham, and Barr then undertook to determine genetic sex from skin biopsies in persons with hermaphroditism and related conditions. They found this procedure reliable, simple and safer than laparotomy.

Their findings confirm the observations of Davidson and Smith. We believe that a determination of genetic sex from a peripheral blood film can be made with a high degree of accuracy. The procedure is simple, rapid and requires no surgical manipulation. Special equipment and technical assistance for processing and staining histologic sections are unnecessary.

**Summary.**—The present study confirms the findings of Davidson and Smith that the polymorphonuclear leucocyte of the human female contains a distinctive nuclear sex chromatin appendage. It is suggested that determination of genetic sex from peripheral blood films is accurate and easier than skin biopsy.

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## SKELETAL MUSCLE, ADRENOCORTICAL INFLUENCE ON

N. Padmanabhan

During the past three decades intense work is being carried out on the isolation of the supra-renal cortical hormones and in the study of their physiological effects, on administration in normal

and adrenalectomized animals, with a view to ascertain the functions of the cortex in health and disease. Durrant<sup>2</sup> in 1924 demonstrated that despite the normal appearance of the adrenalectomized animals, their voluntary activity was decreased. This was proved by later workers to be due to the adrenocortical insufficiency. The development of fatigue and its amelioration has been used by various workers for the assay of corticosteroids. Ingle<sup>6</sup> reported that the work performance of normal rats that were given continuous intravenous injections of cortisone and of corticotrophin, increased the work output of the rats by 22.4 per cent and 8.6 per cent respectively. Del Pozo<sup>1</sup> found that cortisone produced enhancement of muscular contractions in cats when injected in the form of cortisone hemisuccinate, a soluble preparation. He also found improvement in the fifth stage of neuromuscular transmission after cortisone hemisuccinate in normal cats. According to him the saline suspension of cortisone acetate was not useful for immediate action. Ingle<sup>5</sup> again reported that the average total work done by adrenalectomized animals which received adrenal cortical extract was greater than the total work of rats treated with optimal amounts of either cortisone or compound F. Ferri et al<sup>3</sup> observed that adrenalectomy caused a marked decrease of the glycogen, a less marked decrease of adenosine triphosphate and no appreciable changes in the phosphagen content of muscles. Treatment with adrenal cortical extract and desoxycorticosterone acetate decreased the fall of glycogen rate especially in the heart and in striated muscles. It does not affect the loss of adenosine triphosphate.

Ingle et al<sup>7, 8</sup> have continued their studies and found in adrenalectomized eviscerate rats that the presence of the liver and other intra-abdominal organs was not necessary for an effect of cortical extract upon muscle work. Continuous intravenous injection of adrenal hormones improved the work output of adrenalectomized eviscerate rats. Other observations by them<sup>9</sup> demonstrated that the work performance of hypophysectomized adrenalectomized rats is not restored to normal by adrenocortical hormones. However, by adding certain commercial preparations of ACTH to the extract, normal performance was obtained. Some partially purified ACTH material, markedly affected work output in hypophysectomized adrenalectomized rats.

Padmanabhan<sup>10</sup> has studied the effects of cortical hormones and corticotrophin mostly on dogs' muscles and those of humans, and to a less extent on the skeletal muscles of other animals. An attempt was also made to identify the part of the suprarenal cortex related to muscular activity. Methods employed in this work were :

1. Histological studies of the suprarenal cortex in dogs after subtotal neurectomy and high spinal transection respectively.
2. Ergography from the gastrocnemius of dogs under anaesthesia using direct and indirect electrical stimulation.
3. Finger ergography in humans and motor point stimulation after fatigue occurred through voluntary effort.
4. Graded exercise tests in man.
5. Ergography from the gastrocnemius of rats and frogs under anaesthesia.

An attempt was made to identify the part of the suprarenal cortex related to muscular activity. Histological studies showed that induced degenerative paralysis of about 50 per cent of the skeletal musculature produced by sectioning the nerve supply to all the limbs, caused almost a corresponding extent of alteration in the normal appearance of the cells pertaining to the outer one-third of the suprarenal cortex. Many cells of the zona glomerulosa were swollen, losing their columnar shape and cytoplasmic granules, the nuclei becoming more condensed and eccentrically placed in some of the cells. In the superficial layers of the zona fasciculata, many cells or cell columns were affected. The cytoplasm became homogenous or highly vacuolated in these cells, with loss of lipid granules in the cytoplasm and in some cells degeneration and eccentric placement of the nuclei were seen. In addition to the histological changes there was decrease in weight of the gland, decreased sudanophilia of the cortex and increased eosinophilia in the animals. No such changes were seen in the cortex when reflex activity of the paralysed muscles was intact as judged by high spinal transection in dogs. It was concluded that the outer third of the suprarenal cortex is concerned with the function of the skeletal muscle.

The effect of the cortical hormones was sought to be observed at the various points of impulse transmission. It was found that the cortical hormones, corticosterone and 17-hydroxy 11-dehydrocorticosterone exerted beneficial effects (1) directly on muscle, probably by altering

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the membrane permeability of the muscle fibres to favour electrolyte and fluid exchanges with the interstitial fluid and through maintaining the turgescence of the supporting matrix of the muscle whereby a better mechanical vantage could be obtained for the contracting muscle fibres. (2) The hormones are capable of postponing neuromuscular fatigue in dogs and humans, substantiating the work of Del Pozo<sup>1</sup> and (3) they are capable of exerting a beneficial effect at the motor synapses in the spinal cord whereby fatigue in voluntary muscular effort is postponed in man, as shown by finger ergography in humans.

One curious but important fact noted was that cortisone acetate did not benefit the muscle when administered parenterally unless it was sufficiently diluted with saline before injection. This was probably the reason for Del Pozo's<sup>1</sup> observation that saline suspension of cortisone acetate was not useful for immediate action.

Replacement therapy with the cortical hormones after bilateral adrenalectomy in dogs and rats revealed that the muscles which lost the vigour of contraction again showed returning vigour though not to the normal extent. It was concluded that cortisone and 17-hydroxy 11-dehydrocorticosterone are not the only hormones concerned with muscular activity. Ingle<sup>10</sup> found similar observations in this respect and concluded that "cortisone is not the only physiologically important secretory product of the adrenal cortex, if indeed it is a normal secretory product of the adrenal cortex at all".

In dogs, after unilateral adrenalectomy it was found that the muscle work performance which was low following the operation, gradually improved and reached normal in ten days, showing that compensation by the intact adrenal gland was attained by this time. In the dog as well as in the frog, a preliminary stage of hyperexcitability and irregularity in contractions occurred after adrenalectomy. These disappeared very soon on the second day in the frog but endured longer in the dog. Working on normal dogs it was found that a single dose of 75 I.U. of ACTH injected four hours before ergography increased the work performance by 95 per cent though there was a slight contracture in the muscle.

In graded muscular exercises for middle-aged men who were untrained there was a definite improvement in the duration, and ease of work performance when cortisone and 17-hydroxy 11-dehydrocorticosterone were administered in divided doses for two days prior to the exercises. A single dose of ACTH, 75 I.U., injected four hours prior to such tests also caused a beneficial effect. Though there would be an undoubted psychological effect of premedication to a certain extent, the fact that the three hormones gave different degrees of improvement showed that they confer a significant ergogenic effect in human muscular work.

As mentioned earlier, a postponement of synaptic as well as end-plate fatigue in man was observed in the present series, and there was also increased amplitude in ergography in humans. It was concluded that the hormones cortisone and 17-hydroxy 11-dehydrocorticosterone would not only increase the early work performance but also the total work performance by postponing fatigue. ACTH also caused a beneficial effect though less in degree. The descending order of the hormones in conferring a beneficial effect on human muscular work in these tests was found to be 17-hydroxy 11-dehydrocorticosterone, cortisone and ACTH. That 17-hydroxy 11-dehydrocorticosterone is more potent than cortisone was also found in a earlier series of experiments on rats.

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## SKELETAL TUBERCULOSIS, SURGERY IN

M. Natarajan

A survey of the treatment of skeletal tuberculosis during the past 100 years reveals a certain trend of thought. The earliest attitude was that of utter helplessness when the disease was called the 'King's evil'. The disease progressed inexorably, causing increasing debility complicated

by multiple sinuses, amyloidosis and death. We then find a period when heroic attempts at saving the life were made mainly by amputation of the limbs or radical excision for lesions of distal joints. Attempts at radical excision were followed by non-healing of wounds, infection and spread of disease to meninges with a fatal end.

It was at this time that Hugh Owen Thomas of Liverpool propagated his ideas of conservative management of these cases. The importance of constitutional treatment for these conditions was accepted in the early part of this century and this led to a revolutionary change—for the better—in the approach to treatment. Special sanatoria were established for treatment of these cases. By providing absolute rest to the joint and general treatment to improve body resistance a remarkable object was achieved in the number of lives and limbs saved. This necessarily meant a prolonged period of immobilisation which extended upto 3 to 5 years in many cases. In the treatment of bone and joint tuberculosis, this tradition of conservatism has established certain dicta, the total acceptance of which will thwart our progress and condemn many patients to prolonged invalidism, which is crippling physically, mentally as well as economically. The mortality though much less than before was still as high as 20-30 per cent. The prolonged, uninterrupted enforced immobilisation for long periods gave rise to complications like contractures, wasting, renal calculi, epiphyseal arrest and stunting, physically as well as mentally, of children.

The advent of antituberculous drugs raised hopes that we may be able to give up all conservative treatment and eradicate all lesions by the use of drugs alone. These hopes were soon shattered and it became evident that conservative measures are still essential in the treatment and that the drugs can only serve as adjuvant. There has been a dangerous tendency on the part of general practitioners to rely completely on antituberculous drugs and neglect more important measures, to improve the general resistance of the patient and give absolute rest to the joint.

*The Role of Surgery :* Surgery in skeletal tuberculosis may be considered from two aspects :

- (1) Surgery carried out to deal with the late end results of the lesions
  - (i) Arthrodesis
  - (ii) Osteotomy
- (2) Surgery performed during the active stage of the disease
  - (i) Diagnostic
  - (ii) For cold abscess
  - (iii) For paraplegia
  - (iv) Curetting of the lesion.

Surgery was still considered an elective procedure when the lesion was considered quiescent. Such elective surgery consisted mainly of arthrodesis of joints which were in an unsound position of ankylosis. Correction of deformities was done some years after quiescence of the lesion, when ankylosis occurred in a faulty position.

The ideal method of treatment of any joint condition must satisfy certain basic requirements. The treatment has to result in a joint with optimal function. It should arrest the progress of the disease and prevent complications and should be complete in a reasonably short period.

The treatment accepted as best at present aims at sound ankylosis of the joint in good position. Such a standard is obviously far from the ideal to be desired.

The main reason for such an attitude has been the fact that in most cases the articular surface of the joints is badly damaged before the condition is diagnosed. Progress towards the ideal of saving the function of the joint can be only made when we succeed in diagnosing the condition during the early stages, when the infection is yet confined to the synovial stage or when the bony focus is minimal.

*Exploratory Surgery :* The advent of chemotherapy has made this type of surgery safer and possible earlier. While life and limb saving had been the aims in the earlier periods the saving of function of the joints became the aim after the drugs came into use. Attempts at earlier diagnosis were helped by exploratory surgical procedures.

Streptomycin and other drugs have helped us to undertake safely open biopsies of joints to establish the diagnosis early and start treatment with a view to save the function of the joints.

It is now an almost a routine practice to do an open synovial biopsy in all cases of synovial tuberculosis of the knee where the lesion has not spread to the bone.



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Synovial biopsy of the hip joint is also done to establish the diagnosis early when the symptoms and signs are minimal.

Such a procedure, in addition to providing a piece of tissue for histological study relieves the tension of excessive effusion into the joint capsule and thus improves the blood supply to the synovial membrane. It also gives us an opportunity to instil streptomycin into the joint cavity.

*The Role of Surgery in the Treatment of Spinal Tuberculosis:* While the sheet anchor of treatment of spinal tuberculosis is conservative, surgery has a definite place to help total recovery of a patient. The indications for surgery in tuberculosis of the spine can be grouped under the following categories :

1. Treatment of cold abscess.
2. To promote complete quiescence of the disease and prevent reactivation by spinal fusion.
3. For the treatment of paraplegia.

The majority of cases of spinal tuberculosis heal soundly by conservative treatment. In children the vertebral bodies come together and fuse to form a bony block. In adults spontaneous fusion is not always satisfactory and is much slower. In many cases the adjacent vertebral bodies do not come into contact in spite of prolonged immobilisation and on X-ray examination there is a gap between the vertebral bodies; this gap is filled with fibrous tissue or unabsorbed debris and this corresponds to the fibrous ankylosis in other joints. Thus we find that while most of the cases of tuberculosis of spine in children end up in sound ankylosis by conservative treatment alone, a good percentage of cases develop an unsound ankylosis. No case which has healed with unsound ankylosis can be considered to have been permanently cured. Such cases, in course of time, go in for increasing deformity and reactivation of the disease. To obtain a total recovery of the patient such cases with unsound ankylosis should have surgical fusion by operation. The purpose of spinal fusion is to make the affected part of the spine a mechanically sound weight-transmitting column. The timing of the operation should be carefully considered as it should not be undertaken till the lesion itself clinically and radiologically enters the quiescent stage.

There are again some cases where after a suitable period of conservative treatment, the lateral half of the vertebra fuses antero-posteriorly by bony block with the corresponding half of the adjacent vertebra, while the other halves remain in a fibrous ankylosis. This results in a scoliotic deformity. The mechanical instability of such a position causes persistent pain in the back even while the disease is completely quiescent. Such cases also need a fusion operation to stabilise the spine. In both these situations the operation is done for purely orthopaedic reasons to provide a sound ankylosis and ensure permanent quiescence of the lesion. Lastly, a special location of the disease as in the upper dorsal and cervico-dorsal regions where a sufficient immobilisation in the ambulatory stage is impossible with a brace, a spinal fusion will be essential.

*Technique of Spinal Fusion:* The technique employed is a modified form of Hibb's spinal fusion.

After accurate localisation of the level of the lesion by preoperative X-rays with a metallic marker on the skin, the spines are exposed including one above and one below the level of the lesion. The spinous processes are excised and the laminae made raw by removing cortical bone. The big raw area thus created is packed with cancellous bone chips taken from the posterior half of iliac crest.

*Use of Homogenous Bone-graft:* In the tuberculosis sanatoria where large numbers of ribs are excised in thoracoplasty operations, I have started using split ribs obtained from such patients as grafts for packing the raw area made in the spine of the patient. This procedure saves time and a second operative wound in the patient. There is very good callus formation by the use of such cancellous bone and the fusion is quicker and sounder.

As facilities of a bone bank are not available with us cases of spinal fusion and thoracoplasty are prepared for operation simultaneously in the twin theatre and the ribs are directly transferred from one patient to the other.

*Paraplegia due to Pott's Disease:* Paraplegia is still one of the most significant complications of spinal tuberculosis. Modern chemotherapy with conservative treatment has almost completely eliminated other complications like miliary dissemination, tuberculous meningitis,

persistent multiple sinuses with secondary sepsis and amyloid disease, leaving paraplegia as the only serious and dangerous complication of the disease. Before the age of chemotherapy the incidence of paraplegia was 11 per cent but now it is much less.

The classical study of Seddon and Butler in 1935 described the causes which produce paraplegia. Two main groups can be differentiated by their onset being early or late in relation to the activity of the disease.

1. Early onset paraplegia associated with primary activity of the disease. This is caused by
  - (a) Pressure on the cord by a tense intraspinal cold abscess,
  - (b) Pressure by granuloma or tuberculous debris,
  - (c) Pressure by bony sequestra or, pathological fracture dislocation,
  - (d) Occasionally a transient oedema of the cord or thrombosis of vessels supplying the cord.
2. Late onset paraplegia ; the paraplegia comes on some years after the disease has become quiescent. This can be caused by
  - (a) A reactivation of the disease,
  - (b) Grossly increasing spinal deformity causing a stretching of the cord.

Sometimes paraplegia is the presenting symptom in the disease especially in adults. There may be slight tenderness over the spine but X-rays do not reveal any bony lesion. Such cases on further observation and on repeated radiological examination often reveal a disease of the interarticular joints, the pedicles or the laminae.

*Treatment* : In children, paraplegia due to Pott's disease has a good prognosis and they all recover if proper immobilisation and chemotherapy are carried out. The prognosis is so uniformly good that Hugh Owen Thomas welcomed the onset of paraplegia in children as it enforced the child to remain in bed with adequate immobilisation of the spine.

In adults also the basis of treatment is immobilisation and conservative treatment. The majority of cases of paraplegia recover by such a conservative regime of treatment.

The paraplegic patient is immobilised, chemotherapy started and a careful watch is maintained to spot any early sign of recovery. Relief from muscle spasms, control of bladder function and recovery of sensations, occur in that order, before motor functions return. If no signs of recovery appear after a reasonable period of conservative treatment one has to carefully assess the points in favour of and against a surgical operation. It is difficult as to state as how long one should wait before deciding that the patient will not recover with conservative treatment. Some authors believe that if there is no evidence of recovery within a month after immobilisation, surgery must be contemplated. Their view is that further delay results in irreparable damage to the spinal cord. There are some who would give conservative treatment for six months before deciding on a surgical intervention.

It would be reasonable to fix the time-limit somewhere between the two extremes. The general condition of the patient is an important factor to be considered but the threat to the viability of the spinal cord and the dangers of a severe paraplegia have to be balanced against the poor reaction of the patient. The next factor to be considered is the completeness of the paraplegia and the presence of a shadow of a tense paravertebral abscess on X-ray. On the whole, it might be better to operate on a few cases that would perhaps recover without operation rather than to run the serious risk of irreparable permanent damage to the cord through hesitation on the part of the surgeon and delay.

Thus the indications for an operation should be—

1. Paraplegia becoming worse or not improving in spite of thorough conservative treatment for three months.
2. Paraplegia already very severe and complete with uncontrollable and exhausting involuntary spasms of the muscles.
3. Paraplegia with a very tense paravertebral abscess as shown on X-ray.
4. Presence of a "spinal tumour syndrome" where the lesion is in the posterior segment.

It must be emphasized that the immobilisation of spine must be uninterrupted before, during, and after the operation.

## Skeletal Tuberculosis, Surgery in

The operative procedures recommended for paraplegia are the following :

1. Costo-transversectomy
2. Laminectomy
3. Antero-lateral decompression.

In his description of paraplegia Pott wrote in 1779, "The remedy for the most dreadful disease consists in procuring a large discharge of matter and in maintaining such discharge until the patient shall have recovered the use of his legs". Thus, in giving the description of the disease Pott also laid the foundation for the surgical drainage of the condition.

1. *Costo-transversectomy* : This is indicated when there is a tense spherical paraspinal abscess. It is a simple procedure. Through a midline incision with its centre over the level of lesion the medial 2 inches of one or two ribs and the corresponding transverse processes of the vertebrae are excised. The cold abscess is opened by blunt dissection, then drained and completely evacuated of all pus and debris. The wound is partially closed with a gauze wick left in for 48 hours.

2. *Laminectomy and Spinal Fusion* : This operation has a limited application in cases where the lesion is in the posterior segment of the vertebrae and when there is no obvious tense abscess shadow, particularly in cases of the "spinal tumour syndrome" type. The pressure in these cases is due to granulation tissue or pus. Laminectomy should be followed by a spinal fusion either in the same sitting or at a second operation.

3. *Anterolateral Decompression*: This procedure also described as lateral rachotomy is a more serious type of surgical intervention. The first step is a costo-transversectomy of two ribs and corresponding transverse processes. The cold abscess is evacuated completely. The pedicles of the vertebrae are nibbled off. Using the intercostal nerves as guides, the lateral surface of the cord covered with the dura is exposed. The cord is lifted up by using the nerve and the posterior surface of the vertebral body exposed. The tuberculous focus in the body is scraped and all debris, sequestra and granulation tissue removed. Local streptomycin is applied and the wound closed.

This operation can be completed with an anterior spinal fusion. Chip grafts from iliac crests are applied to the vascular, healthy, vertebral bodies and the wound closed. Thus, decompression for paraplegia is combined with a stabilising spinal fusion which shortens the total period of treatment to a large extent.

*The Role of Surgery in Tuberculosis of the Hip Joint*: Apart from minor surgical procedures in relation to cold abscess the main indications for surgery in tuberculosis of the hip are :

1. Operation to permanently protect the disease joint from re-activation—arthrodesis.
2. Operation to correct deformities—osteotomy.
3. Operation to equalise leg length when there is excessive shortening.
4. Rarely, as a life-saving measure—radical excision.
5. Curetting of an active lesion.

*Arthrodesis of the Hip Joint*: The production of a mechanically sound fusion of the hip has been a difficult operative problem as the articular surfaces are at great depth. The fear of spread of infection and non-healing of the wound, kept the surgeons away from entering the joint cavity. An extra-articular procedure was adopted of which the ileo-femoral arthrodesis has been the favourite method till now. In this method, a bone graft was placed between the ileum above the acetabular roof to the greater trochanter. This method is accompanied by a mechanical defect in that the bone graft being above the joint, is under a tension strain as the weight bearing tends to adduct the joint. The graft gives way either at the upper or the lower end. In children the greater trochanter being mostly cartilaginous the graft often fails to take in its distal end.

An architecturally sounder method of ischio-femoral arthrodesis was introduced by Brittain by placing the graft under compression through an osteotomy gap into the ischium below the acetabulum. This produces better fusion, particularly in children.

*Para-articular Arthrodesis* : As the risk of opening the joint capsule is much less these days due to the availability of the antituberculous chemo-antibiotic therapy, one can boldly approach the joint as closely as possible, in an endeavour to produce a good arthrodesis.

The method of arthrodesis followed at present can be described as para-articular as the graft used is placed directly on the neck of the femur. After exposure of the hip joint by a

posterolateral approach, the capsule is completely excised from the superior aspect of the joint, the cortical bone is removed from the exposed part of the head and upper aspect of the neck of the femur and any sequestrum in the joint cavity is removed. The greater trochanter is chiselled off obliquely at the base. The bone piece is rotated through an angle of  $180^{\circ}$  and laid on the raw surface of the neck and its tip is jammed into a groove made in the acetabular rim. This contact of raw bone surfaces gives rise to good callus formation and a strong bony bridge forms between the acetabulum and the trochanteric region, in continuity with the neck of the femur.

The results of such a para-articular arthrodesis have been uniformly good in all the cases done so far and the post-operative period has been almost afebrile and primary healing of the wounds has been obtained. This has been possible by providing a pre- and post-operative course of streptomycin.

*Surgery as an Adjuvant to Chemotherapy*: While chemotherapy has been playing an adjuvant role to conservative treatment as well as to elective surgery, it is becoming clear that surgery can be made to play an adjuvant role to the chemotherapy in the treatment of skeletal tuberculosis.

It has been recognised that while skeletal lesions diagnosed in the very early stages responded very well to combined conservative measures and chemotherapy, cases discovered late do not respond so well. A study of the microscopic pathology of the tuberculous lesion will explain this difference in response. While cellular response and local hyperaemia are characteristic of the early stages of tuberculous pathology, in the later stage the characteristic picture is that of endarteritis obliterans and ischaemic necrosis, together with fibrotic response surrounding the focus. It follows that ischaemic necrosis is part of the pathology of tuberculosis and unless a pathway is opened surgically, antibiotics cannot have any access to the lesion.

Surgery then can play an adjuvant role to break down the barrier surrounding the tuberculous focus in bones and produce a local hyperaemia and help the chemotherapeutic drugs to act on the focus. Thus we see the return of the more radical methods of local attack on the lesion helped by chemotherapy and in turn helping the chemotherapy to reach the site of lesion and exert the bacteriostatic effect on the tubercle bacilli. We have thus reached the stage when, with the full benefit of constitutional treatment and chemotherapy, we can approach the skeletal lesion and curette it completely.

*Curetting of the Active Lesion*: In the spine, the lesion is approached by a costo-transversectomy in the thoracic region and transversectomy in the lumbar region. The vertebral body is approached and any para-vertebral abscess evacuated. The lesion in the vertebral body is curetted and all granulomatous tissue removed. When healthy vascular bone is left, the raw area is packed with pieces of cancellous bone from the iliac crest, bridging the adjacent vertebrae. This method results in a good solid anterior spinal fusion.

Such a drastic procedure has been advocated by enthusiasts like Wilkinson for all cases of tuberculosis of the spine. Wilkinson advocates a conservative treatment of 3 to 4 months in adults before central curettage is undertaken. In children, particularly for lesions in the dorsal region, when the destruction is more rapid and extensive, conservative treatment is given only for a month and then curetting is undertaken. A similar regime is advocated by Mukopadhyaya of Patna.

The average duration of treatment in such cases is reported to be 12 months. It appears unjustifiable to subject every patient to an operation but such curetting can certainly be done in cases which continue grumbling activity inspite of prolonged conservative treatment. Another group of cases where such a treatment will be justified is those cases where there is a reactivation of old lesion.

A similar curetting can be done for tuberculosis of other joints like the elbow and the hip. Wilkinson has advocated partial synovectomy and curetting of early lesions in the hip. Such a procedure in his hands has given a healed lesion with a good  $90^{\circ}$  flexion movement in the hip. The follow-up period is too short to pronounce a judgment about the curetting procedure particularly in a weight-bearing joint like the hip.

The procedure of curetting the active lesion is so diametrically opposed to the principles and practice of treatment haloed by tradition that it can hardly be accepted on the basis of such

## Skin Hyperpigmentation in Parasitic Intestinal Infestations

short-term follow up. But further developments of such methods will certainly revolutionise the treatment of skeletal tuberculosis ; therein lies a great danger because attempts to cure the patient by exterminating the bacilli in the local bone lesion may lead to a precarious recovery if the constitutional treatment is neglected. With the combination of the old knowledge and the development of the new, a new chapter in the treatment of skeletal tuberculosis is opening. At this juncture it is essential to recollect once again the fact that tuberculosis is a constitutional disease of which the skeletal lesion is only a local manifestation and that tuberculosis is a social disease. The patient had come to the hospital because a deep-seated tuberculous lesion became active and bacillaemic in his old house and social conditions thus producing the skeletal focus. If we allow the patient to return to the same environment, his vitality will go down, the newly acquired resistance will be lost and the lesion would most likely relapse. This only emphasizes the need for a long-term rehabilitation which is well within the province of social medicine and the establishment of a welfare state.

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## SKIN HYPERPIGMENTATION IN PARASITIC INTESTINAL INFESTATIONS

K. C. Sahu

Hyperpigmentation was observed in a series of 21 patients, suffering from various intestinal parasitic infestations. These intestinal parasites produce directly or indirectly starvation, nutritional deficiencies and digestive upsets. Lack of proteins results in shortage of tyrosinase and tyrosine and similarly protein lack might result in tissue shortage of cystine and glutathione with consequent pigmentation. The pigmentation might be due to all melanin being present in the black form.

Diagnosis in each case was established by repeated stool examination by ordinary and in some cases by concentration methods and by elimination of other diseases like Addisons' disease, syphilide, etc. by appropriate investigations. Out of 21 cases 11 were due to amoebiasis, five due to ascariasis and five due to ankylostomiasis. The incidence was highest in the age group 20-30, the percentage of incidence being 47.6 per cent. Males constituted 71.5 per cent of the cases observed, the incidence of males to females being approximately in the ratio of  $2\frac{1}{2}$  : 1. One case occurred in a female child.

The pathogenesis of the condition is discussed.

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## SKIN TUBERCULOSIS AND ITS RELATION TO PULMONARY TUBERCULOSIS

K. C. Sahu

Skin tuberculosis is not infrequent in this country. Out of nearly 18,000 cases attending a skin clinic in Calcutta, the percentage of skin tuberculosis was nearly 2.5 to 3 per cent.

Among two hundred cases of skin tuberculosis reported here, 45 per cent showed pulmonary involvement. The necessity of X-ray examination of the chest in all cases of skin tuberculosis is therefore stressed.

Though skin tuberculosis is usually considered to be due to avirulent type of tubercle bacilli yet in the present series of cases reported, there were 55 cases of lung affection, 13 cases of pleural thickening, 37 cases of gland enlargement, one case of miliary tuberculosis and 2 cases of meningeal tuberculosis. Quite a number of cases were due to virulent types of bacilli. Skin tuberculosis ought to be taken in such perspective and managed accordingly.

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## SKIN AND VENEREAL DISEASES

K. C. Kandhari

Dermatology and venereology, specially the latter, have made such progress in the last fifteen years that in certain countries the problem of venereal diseases is considered to be almost completely solved. Much of this has been achieved by penicillin and other potent antibiotics which changed the face of this problem in having so short, effective, and comparatively non-toxic treatment. The correlation of views has been thorough and complete through agencies like the World Health Organisation.

In the field of dermatology, the trend of thought has been to shift from the purely morphological diagnosis to seeking of the aetiological factors in the disease process. There have been attempts to correlate skin diseases with systemic disorders.

In therapeutics of the diseases of the skin there has been great advance in some spheres, such as the treatment of tuberculosis and generalised bullous eruptions of pemphigus and allied conditions, and of lupus erythematosus. There has also been of late revival of certain surgical procedures in the management of selected skin disorders. Greater use has been made of antibiotics, antihistamines, and steroids in many conditions. Experience gained in their use and their limitations are described in the following pages.

Antibiotics have been divided into two groups:

### *Bactericidal (Group I)*

and

### *(Bacteriostatic Group II)*

Penicillin  
Streptomycin  
Bacitracin  
Neomycin  
Tyrothricin

Tetracycline (Achromycin)  
Oxytetracycline (Terramycin)  
Chlortetracycline (Aureomycin)  
Chloramphenicol

When antibiotics are to be used together, group I members act as synergists but group I and II less so, and sometimes as even antagonists.

*Erythromycin group* of antibiotics are valuable drugs. Erythromycin was discovered in 1952 and is similar in action to penicillin, and even somewhat superior against Gram-positive cocci. It is ineffective against Gram-negative organisms except diplococci. It is a useful alternative in cases where penicillin sensitivity is a problem.

*Carbomycin* is similar in action but weaker.

*Spiramycin* is prepared from streptomycetes *ambifaciens*. This has been tried in cases of gonorrhoea and non-specific urethritis with good results and with no serious toxic reactions.

*Oleandomycin* is still another addition, similar in action to erythromycin, but not superior to it even when combined with twice its weight of tetracycline and sold under the proprietary name of *sigmamycin*.

*Penicillin 'V'*: Penicillin 'G' has been the main brand so far used both as such and in combination as repository preparation but its drawback had been that it could not be administered by mouth, being destroyed by hydrochloric acid of the gastric juice.

Penicillin 'V' has now been in use by the oral route and tried in many conditions and it has shown evidence of good action. It has been specially recommended for use in infant patients of congenital syphilis to avoid severe and sometimes fatal Herxheimer reaction by treatment with penicillin 'G'.

*Tyrothricin and Bacitracin*: These are antibiotics mostly used locally, as when given systemically they have proved very toxic. They are useful in pyogenic dermatoses and infective eczema.

### **Special Points in the use of Antibiotics in Dermatology and Venereology**

*Local Use*: It is now proved beyond doubt that like sulphonamides penicillin and streptomycin applied to the skin result in sensitization in a number of cases. Broad spectrum antibiotics are preferable and are almost similar in action to each other when applied locally. They should however, not be used for more than 5 days or so, to avoid risk of sensitization still likely to occur in some cases and markedly so in seborrhoeic and eczematous patients. More useful than that are antibiotics e.g. tyrothricin, neomycin and bacitracin which for their toxicity are not commonly used systemically.

*Choice of Antibiotics*: So far as the skin infections are concerned there is not much to select from the wide range of antibiotics which are all useful enough. However, in certain special

## Skin and Venereal Diseases

conditions, e.g. otitis externa, and in subpreputial sores or chronic ulcers which have persisted long enough, there is usually growth of pyocyanus and local use of neomycin or of polymixin is advised in preference to others.

*Internal Use of Antibiotics* : Cases of deep mycosis, e.g. actinomycosis, respond to large continued doses of penicillin and broad spectrum antibiotics of the tetracycline group, and lately results with erythromycin have been good enough. Some of these cases and those of athlete's foot and moniliasis, are occasionally aggravated on administration of antibiotics. In the intestine profuse growth of *Candida albicans* (monilia) is reported when antibiotics are administered for any length of time, for any purpose. This is what prompted the manufacturing chemist to put in the market vitamin-fortified preparations with desperate attempts to prevent it, though with variable results, and has also brought into use antibiotics like mycostatin for use against fungi, still with variable results.

*Use of Antibiotics in Non-infective Dermatoses* : Time and again, trials have been made, with large and lengthy dosage in diseases e.g., pemphigus, dermatitis herpetiformis, herpes zoster and lichen planus. There have been good effects noticed occasionally, perhaps by elimination of secondary infection, but on the whole results have been discouraging.

*Use in Venereal Diseases* : Penicillin still holds the place of pride in the treatment of syphilis and gonorrhoea, though all other antibiotics including the newer ones like spiramycin and erythromycin are also good to a varying degree. It should however, be remembered that streptomycin has no effect on syphilis. Terramycin and Aureomycin have been tried and proved useful in early cases of lymphogranuloma venereum. Chloramphenicol is equally useful. Streptomycin given in cases of granuloma inguinale has proved good.

**Antihistamines** : Earlier hopes about antihistamines have not been substantiated, and it is found that they are more useful in urticaria where response to allergenic stimulus is mostly by vascular dilatation. The cellular response of epidermal cells as in eczema is not checked except indirectly through control of pruritus by their sedative side action, wherein lies their greater use even in non-allergic but itchy dermatoses. They are however, useful in certain types of constitutional eczema e.g., infantile eczema of children.

Locally used they are almost ineffective in controlling the allergic process. When given by parenteral route there is greater effectiveness with lesser dosage, and this method should always be tried in intractable cases. Intravenous injections given slowly mixed with normal saline have also been tried and have controlled some serious and difficult cases with good effect. Children tolerate antihistamines well, and a child of 12 years can take full adult dose.

The side effects, e.g. drowsiness, have been successfully controlled by giving amphetamine 5 mg 20 to 30 minutes before administration of the antihistamine.

Apart from the toxic action of antihistamines in the form of giddiness, nausea, tinnitus, gastrointestinal irritation, etc. it has been found that some patients become sensitive to certain antihistamines and eczematous response occurs on topical use of these drugs. Conventional remedies used for allergic dermatoses e.g. calcium, vitamin C, and recently introduced steroids are known to have synergic action, when given with antihistamine drugs. Prolonged use of antihistamines has been known to produce aplastic anaemia.

With greater use of synthetic drugs and with greater industrialisation, the risk of sensitization has increased manyfold. Steroids and parenteral antihistamines are the drugs most used today in these cases.

In American literature, the term 'generalised neurodermatitis' and Besnier's prurigo have all been grouped under 'atopic dermatitis' which is now referred to as generalised papular dermatitis from any cause.

In infants where milk is incriminated as a responsible allergen, powdered soya bean flour mixed with water and sweetened with sugar is given as a substitute for milk. Equally important as food factors in the diagnosis of cutaneous allergy, is the search in all cases for septic foci anywhere in body or on skin surface, worms in intestine, and previous cutaneous infection with fungus, or with scabies, and investigations carried out may also include exposure to sunshine and dust. In fact to our minds there has been no answer so far as to why the usual site for infantile eczema in a baby, is the face? In isolated cases of infantile eczema I have noticed that children exposed to sun get severer and extensive lesions on the parts exposed. The problem of solar dermatitis and photosensitization has been further investigated and certain substances

are known to aggravate or initiate inflammatory response of the skin on exposure to sunshine, e.g. porphyrins, anthracene and sulphonamides, the last one being more important because of its liberal use in practice. Photosensitization by sulpha drugs was first reported by several workers about 2 decades ago, sensitization occurring after systemic and local use and the areas involved were mostly those which are exposed to the sun e.g., face and hands. This increase in light sensitivity due to sulpha drugs has been suspected to be one of the factors in production of lupus erythematosus though not agreed to by others. But the majority of cases showing lesions of chronic lupus erythematosus on exposed parts, its greater incidence during recent years, and its alleviation by drugs which are supposed to reduce light sensitivity support this view strongly, and further research on this point is indicated.

Recently tranquillizer drugs e.g., chlorpromazine meprobamate and benactyzinc, have been observed to cause photosensitization when administered systemically. Protection from photosensitization has been attempted by systemic use of certain drugs, particularly mepacrine, and now chloroquine group of drugs. Nicotinic acid or amide, and vitamin B<sub>12</sub> have also been suggested. Locally applied substances give protection, acting as a 'sun screen'—such substances are titanium dioxide, salol, tannic acid, quinine sulph. and para-aminobenzoic acid (PABA) incorporated in lotions or ointments. Some antihistamines applied locally in a cream or ointment form achieve the same results.

**Endocrines.**—Greater use has been made of corticosteroids and adrenocorticotrophin in various dermatological conditions, and their beneficial result has been established in many skin diseases, though in simulation with their use in many systemic diseases, the good effect that accrues from their use does not last long, and there is return of the disease process on their withdrawal. Nevertheless they are useful, to bridge over critical stages of many serious dermatoses and their judicious use has proved a significant advance in treatment even for palliative relief. They are being used with great advantage in many serious diseases, involving the skin, e.g. acute and subacute lupus erythematosus, scleroderma, and dermatomyositis, especially acute cases, in generalised vesiculo-bullous eruptions of chronic and fatal nature e.g., pemphigus and pemphigoid, and in severe allergenic and toxic states e.g., generalised eczema, atopic dermatitis, giant urticarias, exfoliative dermatitis and Stevens Johnson's syndrome. They are also used in arthropathic psoriasis, wide-spread lichen planus and sarcoidosis.

**Local use :** Employed locally there is beneficial effect in alleviation of pruritus and inflammatory oedema, of allergenic or non-allergenic nature. Compound 'F' or hydrocortisone is useful when employed for topical use in 1 to 2.5 per cent strength mixed in a suitable base. Lately fludrocortisone has proved to be many times more potent and effective. These are used alone or in combination with antibiotics, e.g., neomycin, bacitracin, etc., to combat concomitant infection. Cortisone as such has no action when applied locally, although it is useful when applied to the mucous membranes, e.g., in severe conjunctivitis.

Of late topical use of steroids has been extended to the treatment of burns, keloids, lichen simplex et chronicus of Vidal, alopecia areata, chondrodermatitis nodularis, etc. by local injection of hydrocortisone in some, and by local rubbing in others.

Steroid therapy in dermatological disorders requires fullest consideration of necessary dosage schedules, toxicity and withdrawal symptoms. There should be gradual withdrawal to fix a maintenance dose, or to stop medication in a manner similar to their use in systemic disease. Contra-indications to their use in diabetes mellitus, certain forms of tuberculosis and peptic ulcer, are required to be borne in mind.

With further search for better products, with lesser toxicity, synthetic compounds, equivalent in action to cortisone and hydrocortisone were evolved. They have been put on the market as 'prednisone' and 'prednisolone' and are belived to be 4-5 times more potent in their action. They are thus administered in 1/4th to 1/5th of the dosage of corticosteroids. Their lesser toxicity and greater efficacy have extended their use in dermatological conditions where steroids are indicated and they are also given to patients for domiciliary treatment without much risk. They are used locally in suitable ointment base.

If corticosteroids are given for a long time then along with other effects of overdosage, e.g., sodium retention with oedema and high blood pressure, there is negative calcium balance with resultant osteoporosis in which nor-testosterone (a new analogue of testosterone) is advised to be



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given and this can be of great help where prolonged use is anticipated as in conditions like pemphigus and subacute lupus erythematosus.

Apart from steroids, use is made of other endocrine hormones in various dermatological conditions, e.g. testosterone is used for senile pruritus of male climacteric, and recently in pruritus of obstructive jaundice. Use of oestrogenic hormones, in acne and alopecia of the scalp, and that of thyroid in scleroderma, ichthyosis, myxoedema and menopausal pruritus is well-known. Gonadal hormones can be administered systemically but are found equally effective when applied locally in the form of an ointment. There is absorption from the skin of these hormones, to cause generalised effect. Few of my cases developed gynaecomastia following rubbing of a stilboestrol ointment in the scalp.

**Vitamins.**—A belief has been held for years about deficiencies of certain vitamins affecting the skin adversely and causing different types of dermatoses or mucosal changes.

*Vitamin A* : Vitamin A is held responsible for squamous metaplasia of all epithelium, and deficiency of this vitamin has been known to affect the skin by causing hyperkeratosis, although recently this view has been disputed, and investigations carried out by the Medical Research Council of Great Britain failed to produce such lesions in a number of cases with diets deficient in vitamin A. It was later suggested from research carried out at Oxford that the effects of vitamin A deficiency may in fact be due to the deficiency of essential fatty acids which act as vehicle for carriage of vitamin A. Even deficiency of vitamin C is found to result in roughening of the skin.

Nevertheless, vitamin A administration has been known to cause relief in phrynoderma, pityriasis rubra pilaris, and Darier's disease, and in certain other diseases like acne, eczema, keratosis pilaris, keratosis plantaris et palmaris and kraurosis vulvae it has been tried with uncertain results.

*Vitamin B-complex* : Deficiency of this vitamin is associated with many skin and mucous membrane disorders, e.g. nicotinic acid deficiency causing pellagra, riboflavin deficiency causing angular stomatitis, conjunctivitis, cheilosis and nasolabial dermatitis. Deficiency of other factors such as biotin, pantothenic acid, paraminobenzoic acid, on experimental evidence have led to premature greying of the hair and of scaly dermatitis in animals but these results have not been found in human beings and a definite pattern of dermatosis not known to be produced.

Vitamin B complex however, is used in varied dermatological conditions, e.g., pigmentary disorders, particularly those associated with photosensitization, seborrhoeic dermatitis, acne vulgaris, and stomatitis. In stomatitis it is my experience that some unexplained chronic cases with fissuring of the tongue, which do not yield to oral or intramuscular therapy respond to intravenous injections of the B complex.

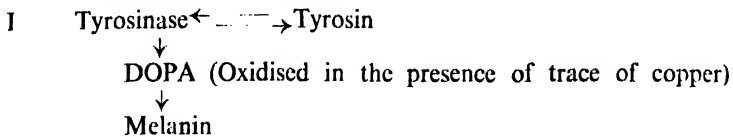
*Vitamin C* has been tried in conditions of increased capillary permeability and in allergenic conditions. Lately it has been used for pigmentary disorders as it is believed to cause inhibition of melanin formation and affects the DOPA reaction. It has also been used in large doses in pemphigus, lupus erythematosus and exfoliative dermatitis where lower blood levels have been noticed by many, although other authors believe it to be the result of such conditions.

*Vitamin D* : Deficiency of vitamin D is not associated with the production of any skin disease but in certain conditions like lupus vulgaris and some forms of localised progressive tuberculosis of skin, calciferol (vit. D<sub>2</sub>) has proved very effective when given orally or parenterally. In nontubercular conditions, e.g. chilblains, lupus pernio and sarcoidosis it has doubtful action. Recently synthetic vitamin D<sub>3</sub> is available and is claimed to be more effective than D<sub>2</sub>. It requires further trials.

*Vitamin E* is antioxidant and is used in chronic indolent leg ulcers and trophic ulcers of leprosy. It has been used in collagen diseases such as lupus erythematosus and granuloma annulare with uncertain results.

**Pigmentary Disorders.**—Modern concept of pigment formation in human skin has undergone a considerable variation of thought and Bloch's theory of melanoblasts as being only modified basal cells has been doubted by Masson who believes that dendritic cells are functionally and genetically different from basal cells and are nervous in origin. This has been confirmed by Billingham. Similarly the existence of DOPA oxidase has been doubted and the present concept of pigment formation has been put forth by Lerner and Fitzpatrick (1950), that under the influence

of an enzyme tyrosinase, tyrosine is first oxidised to DOPA (dihydroxyphenylalanine) which is further oxidised to melanin.



- II The oxidation of DOPA to melanin is interfered by reagents which combine with copper, e.g. BAL (British antilewisite), and
- III This inhibition is reversed by addition of an excess of cupric ions but not by ions of other metals.

Clinically inhibition of pigmentation may follow excess of SH group, the use of BAI, or of thiouracil (which contains SH group) and by excess of vitamin C. Locally applied ointment containing 33 per cent concentration of monobenzyl ether of hydroquinone in an ointment base, caused depigmentation of pigmentary patches caused by melanin.

*Some of the factors influencing pigment formation :*

Factor	Action involved in pigment-forming cycle	Result
1. Diet deficient in tyrosine	Lesser raw material with lesser finished product (melanin)	Depigmentation (noticed in animals)
2. Pellagra	Obscure, but explained as destruction of SH group during acute dermatitis	Increased pigmentation
3. Sun-tanning	(a) Ultra-violet rays catalyze oxidation of tyrosine to DOPA (b) Decrease in concentration of SH group in epidermis after irradiation (c) Increased melanin formation due to raising of temperature of skin.	Increased pigmentation
4. Administration of heavy metals	They combine with SH group and remove their inhibitory effect on melanogenesis	Increased pigmentation
5. Post-inflammatory lesions	Destruction of SH group in cells	Increased pigmentation

Connected with the problem of pigmentation has been the treatment of vitiligo and other depigmentary lesions, and recently reports of El Mofty in Egypt, in treatment of vitiligo by extracts of the seeds of plant *Ammi majus*, Linn, have shown encouraging results in larger number of cases though prognosis in an individual case is unpredictable. Active principles (ammidine and ammoidine) of the plant are supposed to act by inactivating SH groups. Effect has been produced both by systemic administration and local application on the skin. Recently El Mofty (1957) has altered his original technique by giving in addition to 8-methoxy psoralen, copper sulphate, 15 mg daily by mouth, in order to potentiate tyrosine activity.

**Dermatomycosis.**—Advance has been made in culture of fungi, not only from skin lesions but also from mucus membranes, and from other affected lesions and organs. There has been good deal of work done in the United Kingdom and number of cases of favus and trichophytosis have been discovered. It is stated that *Trichophyton rubrum*, *Aspergillus fumigatus* and yeast-like fungi are common in Britain, *Trichophyton mentagrophytes* and *T. rubrum* are more commonly involved in cases of athlete's foot and *T. sulphureum* for ringworm of scalp. In India except in large centres, e.g. at the Calcutta School of Tropical Medicine and at the Armed Forces Medical College, culture work on fungi has not been taken up as a routine, although there is great need for the same due to large number of dermatomycotic cases. It is therefore, not certain as to what type of fungal infection is most common, in the absence of authentic reports.

## Skin and Venereal Diseases

Certain drugs are available for the treatment of dermatomycoses e.g., ointments containing unsaturated fatty acids like propionic and undecylenic acids which act as inhibitors to the growth of fungus and which have been usefully employed in mild cases or cases requiring prolonged therapy.

Nystatin has been used both internally and locally in an ointment base. It is an antibiotic with inhibitory action on the growth of fungus, chiefly of monilial type.

Systemic use of stilbene derivatives has been made in successfully treating blastomycosis. 150 mg of stilbamidine in 200 c.cm of 5 per cent dextrose solution given intravenously, daily for 1-2 weeks shows good effect in the amelioration of the disease.

**Seborrhoeic Diathesis.**—Seborrhoea is no more viewed as a simple infection with *acne bacillus* and *pityrosporon* of *Malassez*. It is considered a diathesis, manifesting itself in different ways at different stages of an individual's life, e.g. milk crusts of the infant, seborrhoea capitis of the child, acne of adolescence, seborrhoeic dermatitis and rosacea of middle age and seborrhoeic warts of the old age, are considered as one long continued story of a special diathesis, which is influenced by various other factors as diet, general habits, heredity, endocrines, infections, psyche and regime of life. Anyone of these factors may be predominant to unleash the trigger mechanism in a susceptible person.

Newer medicines in the treatment of seborrhoea are 'Selenium Sulfide' (Abott) and 'Dermasulph' (Crooks). The action of the former is due to inactivation of free sulph-hydral group and compounds through mercaptide formation and along with this, its detergent action causes a chain of reactions. Clinically good effect accrues, by relief from itching and scaling after 2-3 applications. The action of "Dermasulph" is based on bactericidal and keratolytic action of sulphur in a colloidal state. I have found 'Cetavlon' (Cetremide solution, I.C.I.) a very good detergent and disinfectant for scalp and 1-2 per cent solution, used as shampoo has given good results in cases of seborrhoea capitis.

Adjuvant factors in the management of seborrhoea and acne vulgaris require careful attention to dieting and other factors involved. The use of vitamin B complex in all seborrhoeic conditions is found beneficial. In acne resort can be had to surgical opening of infected lesions, and of X-ray therapy to cut down the gland activity.

**Lupus Erythematosus.**—Diagnostic methods for this condition have improved recently. Finding of 'L.E. cell', a pathognomonic test for the diagnosis of acute and subacute cases has been simplified by finding the cell in capillary blood by finger prick method, rather than resort to sternal puncture or taking of venous blood. Making use of three essential factors in the production of L.E. cells, viz.

- (a) Plasma or serum from patients, with subacute lupus erythematosus
- (b) Nucleoprotein from nuclei of damaged cells (which form the substrate), and
- (c) Active phagocytic polymorphonuclear leucocytes,

Lempert and Berlyne evolved a simple method of taking venous blood from patients with chronic lymphatic leukaemia for the substrate, rather than from normal blood as previously advised by Snapper and Nathan.

Corroborative blood tests found in this disease are, dysproteinaemia, hyper-gammaglobulinaemia, false positive serological tests for syphilis (25-40 per cent cases), increased E.S.R., delayed blood coagulation, leukopenia and acquired haemolytic anaemia. The liver function tests show impaired function.

Although the cause of lupus erythematosus still remains obscure, yet its protean manifestations in remaining chronic and discoid for decades, or becoming systemic and involving many organs, and its showing positive tests for syphilis in nearly half of the cases have resulted in further conjectures about its aetiology.

In the field of its therapeutics corticosteroids have proved a boon in the management of acute and subacute cases and mepacrine is being replaced by chloroquine and other identical preparations in the treatment of chronic discoid variety.

**Herpes Zoster and Simplex.**—The mode of production of the lesions has been discussed and attributed to the release of an H-substance which is also responsible for certain systemic lesions.

Association of herpes zoster and chicken pox virus has been further discussed and production of motor lesions in cases of herpes zoster described. It is now accepted that herpes zoster is essentially an affection of the central nervous system, rather than of the dorsal root ganglia.

In recurrent attacks of herpes simplex and aphthous stomatitis a bi-weekly vaccination on the arm given for 6 weeks with small pox vaccine lymph is reported to have resulted in avoiding a further attacks in number of cases. I have tried this method and have found it useful.

**Pruritus.**—Further studies on the subject have shown good symptomatic relief of this important symptom by application of N-ethyl-o-crotonotoluide (Eurax), by systemic administration of glutethimide (Doriden) or Chlorpromaxin.

**Skin Surgery.**—James W. Burk Jr. (1956) of Springfield, Illinois, U. S. A., and Ervin Epstein (1956) of California U. S. A., have written monographs on “*wire brush surgery*” and “*skin surgery*” and introduced dermabrasion as a treatment in removal of scars and blemishes due to small pox, rhinophyma, naevi, keratosis and superficial epitheliomata. Even suppurative hydradenitis of axilla has been successfully treated.

In wire brush surgery the revolving wheel of Eller has been replaced by steel wire brushes of various sizes and diameter. Dermabrasion has been mentioned as a simple procedure to be carried out under local anaesthesia and which could be done on in the office. J. T. Ingram (1957) and Patrick Clakson (1957) while reviewing this work have further recommended this treatment in various disfiguring dermatological disorders and the latter author has recommended application of proper asepsis and general anaesthesia. Proper selection of cases and repeated dermabrasion are recommended to avoid failures. This treatment first started by Iverson as sand paper surgery was perfected by late Dr. Kurtin and developed by Burk, Eller and Epstein, and has now been employed by many dermatologists and plastic surgeons with great advantage.

**Chemosurgery.**—Methods of chemosurgery have been developed, and topical use of podophyllin has been made in treating conditions like lichen simplex chronicus, 5 per cent powdered resin being used in compound tincture of benzoin. 36 out of 38 cases showed improvement in a series tried by Balsero of Sydney. In my own clinic at Amritsar I have tried combination as below for these cases and of chronic lesions of lichen planus hypertrophicus with encouraging results.

Phenol	..	..	..	..	..	..	..	1	Part
Chloretone	..	..	..	..	..	..	..	1	Part
Acid salicylic	..	..	..	..	..	..	..	4	Parts
Compound tincture of benzoin	..	..	..	..	..	..	..	12	Parts
Acetone	..	..	..	..	..	..	..	12	Parts
Chloroform	..	..	..	..	..	..	..	70	Parts

Solution of commercial formalin (1 in 10 dilution) is tried for hyperidrosis, palmaris, et plantaris and pure trichloroacetic acid has been applied in the treatment of warts, molluscum contagiosum and in freshly developing papulo-nodules of lupus vulgaris.

**Cytodiagnosis.**—One of the remarkable methods of diagnosis in certain dermatological conditions was developed by Tzanck (1948). This method called ‘*immediate cytodiagnosis*’ is based on obtaining pathological elements for study by scrubbing of the base of lesions e.g., a developing bulla of pemphigus or dermatitis herpetiformis. This method has been confirmed and further developed by Rook and Whimster in England (who also separated cases of pemphigus from pemphigoid) and other workers. It was shown that the main characteristic of pemphigus was acantholysis of epidermal cells, which did not occur in dermatitis herpetiformis or other bullous eruptions. Jarret (1957) has however shown by using fluorescent microscopy that acantholysis cannot be used as an absolute criterion to distinguish pemphigus from dermatitis herpetiformis. Cytodiagnosis is now employed as a method in the diagnosis of developing epitheliomas of skin.

**Soft and Super-soft X-rays.**—Work in this field really comes under the radiotherapist and it may suffice to mention here that greater use is being made of these lesser voltage rays in dermatology because of greater safety and yet equal efficacy in a number of dermatoses. Supersoft (5-40 KV) and Soft X-rays (40-120 KV) are used.

**Ointment Bases.**—Vehicles for local medication have been sufficiently improved by preparations from polyethylene glycols (Carbowax) which have cleaner application and easy washing from the skin. Successful use has been made of diamino-diphenyl sulphone (D. D. S.) in the treatment of dermatitis herpetiformis. The drug is administered in tablet form and the dosage adjusted according to body weight (1-2 mg per kg), given for 6 days in a week has proved superior to arsenic or sulphapyridine in controlling the disease in few weeks.

## Skin and Venereal Diseases

**Venereology.**—Great advances have taken place in the field of diagnosis and treatment of venereal diseases during the last two decades. In India no proper surveys have been conducted about venereal disease and every institution has its own figures. With the advent of potent antibiotics and with their promiscuous use the problem of V. D. has apparently become less severe though it is difficult to say so, as some of the cases seen are not typical, and the book descriptions of over a decade ago or so, do not fit in. Most of the cases are masked, with paucity of signs and symptoms. It has also been noticed that there are cases showing a change in the incubation period of the disease. Lodin (1955) reported 5-6 per cent cases of gonorrhoea showing an incubation period of about 14 days. At the first International symposium on treponematoses low incidence was reported of early syphilis, with continuing high figures of late and latent cases. It was also conjectured that occasionally endemic pinta and bejel on certain areas may act as reservoirs, from which syphilis may spread.

**Resistant and Relapsing Cases :** Even under the best of treatment with adequate dosage of appropriate antibiotics, it is found that both in syphilis and gonorrhoea, a small number of cases always proves resistant to treatment or may relapse after apparent cure. The causation ascribed is, resistance against the drug and inadequate dosage or inappropriate choice of the drug. Such resistance or relapse in cases of urethritis has brought forth to light the problem of non-specific urethritis which is occupying the attention of all workers on venereal diseases.

Cases of nonspecific urethritis (NSU) are broadly classified into bacterial and abacterial and the aetiology of the latter still remains obscure, though mycoplasma (pleuro-pneumonia like organisms) first reported by Harkness and later corroborated by other workers, although not grown on tissue cultures, continue to be doubted. They are even believed to be normal saprophytes of healthy urethra, which increase in conditions of inflammation from other causes, e.g. gonorrhoea.

Some of the non-bacterial cases have been traced to infection with trichomonas, and considerable amount of work has been done in this respect to find out the epidemiology of trichomonas infection by improved methods of diagnosis of examining samples of secretion from patients first by smears and later by culture on liquid liver medium, which has proved successful as against trypticase medium tried previously. An incidence of 12.8 per cent to 21.3 per cent was found in gynaecological cases.

Treatment of trichomonas has been tried by oral medication with 2 acetyl amino 5 nitrothiazole (Tritheon), 100 mg tablets 3 to 4 times a day for 6-14 days and by local and systemic use of terramycin and aminotriazole with unsuccessful results. Spiramycin has been tried in non-trichomonal cases of NSU with almost same results as by other broad spectrum antibiotics.

**False Positive STS.**—False positive results with serological tests for syphilis (STS) have been known to occur in some non-venereal treponemal diseases, e.g. bejel, pinta, yaws, lepromatous leprosy, malaria, glandular fever, etc. Of late it was found to occur in about 40 per cent cases of SLE (subacute lupus erythematosus). Finding of false positive results has very often led to putting up quantitative tests, with high dilutions of serum, for greater sensitivity. This sensitivity has been further improved by introduction of purified antigen, cardiolipin, by Pangborn. The Venereal Disease Research Laboratory of the U. S. Public Health Service introduced a flocculation slide test, with this purified antigen and named it as V. D. R. L. test which is in use almost everywhere as a routine test for syphilis and the results are comparable to older tests, e.g. WR and Kahn, and their further elaborations. In 1949 Nelson and Mayer of Mayo Clinic introduced a test which was different from all the previous CF and flocculation tests and was based on the idea of presence of an antibody in syphilitic serum which when mixed with treponema taken from syphiloma of experimental rabbits, made the treponema lose their movement. The test was named 'Treponema pallidum immobilisation test' (TPI) and is very specific, the biological false positives being almost nil. In 1952 Nelson introduced a new test called the 'Treponema pallidum immune adherence test' (TPIA) in which he demonstrated a reaction between human erythrocyte and treponema sensitized by syphilitic antibody, causing the erythrocytes to adhere together.

Further tests were elaborated in which, instead of live treponema, attenuated heat-killed treponemas were used as antigen and instead of immobilisation their agglutination became the basis of the test. This is called 'Treponema pallidum agglutination test' (TPA). It was introduced by Miller and further work on it has been done by Chacko in Madras. So far, results obtained with this test are not found to be superior to ordinary standard tests. Work

is also being carried out by Chacko to prepare a stable, specific antigen from virulent *T. pallidum* strains for intradermal test for syphilis and some success has been reported in testing cases in late stages of the disease. 'Treponema pallidum complement fixation test' (TPCF) first attempted by Noguchi is also being elaborated. Recently, Carpenter Boak and Miller (1956) evaluated the use of TPI and TPIA tests. Out of 3934 of the positive sera from ordinary tests 2148 showed negative results on TPI test (54.6 per cent). This goes to show the highly dependable specificity of these new tests, and on further elaboration these might be accepted as routine tests in the diagnosis of syphilis.

A clinical diagnostic test has been mentioned by Palichszant and Valer (1955) in the latent stages of syphilis, based on changes in the fundus of the eye. Of 219 patients whose optic disc was normal and not elevated, the margin on the nasal side found to be blurred. There is peripapillary oedema and sheathing of some vessels. The author maintains that these changes are diagnostic.

Urethrography in urethral stricture has been done by Mayne to localise the stricture and study its nature. Six cases were studied by instilling contrast medium (Viskiosol 6) in the urethra and taking radiological pictures. Further work is indicated in this connection. Intra-dermal tests have been surveyed in the diagnosis of lymphogranuloma venereum by King et al at Whitechapel Clinic, London, and a survey of infection in the East End of London was done by an intradermal test with yolk sac antigen for the virus of lymphogranuloma in all new patients attending the Clinic, for a period of 13 months. Comparison was made with complement fixation test; 216 out of 1317 (18.4 per cent) cases were positive and out of these 23 gave positive complement fixation test.

Rajam and Rangiah, reporting a series of cases during the last two decades have found greater frequency of inguinal localisation of the disease (92.4 per cent) while Grace reported greater incidence of genital and anorectal cases (72 per cent). They have also reported cases of anorectal lesions, without stricture. It is believed that Frei's antigen prepared from pus from the bubo and grown on egg yolk sac, is more stable and dependable than antigens from the related psittacosis virus.

**Syphilis in Childhood.**—Rajam and Rangiah of Madras, reported 249 cases of acquired syphilis in young infants and children and traced the source of contact to an adult case in an infectious stage. This survey was carried out over a period of 7 years and proved of great value.

Mentioning of Jarish Herxheimer reaction, Holzel has reported death in 10 cases of early congenital syphilis due to this reaction following administration of penicillin. Hepatomegaly and jaundice clinically, and elevated thymol turbidity biochemically, were considered as alarm signals. Hepatic cell injury in some cases may be so widespread that hardly any normal tissue is left.

The dosage of penicillin administered is immaterial and even 100 units 3 hourly could cause reaction. As a precaution administration of oral penicillin 'V' is recommended in all cases of congenital syphilis under 6 months of age; it is considered safe, does not cause reactions.

**Therapeutics.** - Many recent antibiotics have been available and are being tried in the treatment of venereal diseases.

Penicillin 'V' is a useful addition and may be administered in congenital syphilis. Erythromycin may be tried in penicillin-sensitive cases.

The dosage schedules differ but mainly 4.8 mega units for early syphilis and 10-12 mega units for other varieties, is considered adequate. Rajam has mentioned treatment schedules in various stages of syphilis. Arsenicals are not used as a routine nowadays, but in refractory and resistant cases there is no particular reason to withhold them.

Irrigations in nonspecific urethritis with potassium permanganate or mercury oxycyanide solution are recommended in cases not responding to treatment with antibiotics. Although considered obsolete, they are worth a trial in individual cases.

Terramycin vaginal suppositories are used for the treatment of trichomonal infection, but with equivocal results. Oral medication with Tritheon has not been successful.

In the treatment of lymphogranuloma venereum, Terramycin, Aureomycin and chloramphenicol have been used but with no spectacular results and require to be given in large doses and interrupted courses. They are useful in early cases and give symptomatic relief.

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**SMALL INTESTINE**—See STOMACH AND SMALL INTESTINE, SURGICAL ASPECTS OF DISEASES OF

**SMOKING AND CANCER**—See CANCER OF THE NOSE AND THROAT, IN ASSOCIATION WITH TOBACCO SMOKING AND CHEWING

## SPLEEN, CONGENITAL ABSENCE OF THE

V. C. Anguli

1. Congenital absence of the spleen is often part of a syndrome of congenital anomalies consisting of malformation of the heart, partial situs inversus, symmetrical lobulation of the liver and the lungs, and anomalies of the abdominal arteries and veins. In a study of 78 cases of agenesis of the spleen (including 8 new cases), malformations of the heart were observed in 49, 29 of these in association with partial situs inversus. Situs inversus of body cavities or organs was present in 35 cases, and was independent of malformation of the heart in 6.

2. Certain of the malformations, such as symmetry of lobation of the liver and the lungs, can be explained as a result of suppression of laterality in embryonic development. Arterial and venous variations may be dependent on absence of the splenic anlage, or the arterial variations may be the cause of agenesis of the spleen.

3. The time of origin of this anomaly seems to be in approximately the fifth to seventh weeks of foetal life, and this coincides with the teratogenetic period of all of the associated anomalies of the heart, blood vessels, and visceral situs.

4. Agenesis of the spleen is more frequent in males, and is most often observed in infants and children under 3 years of age, owing to the limited span of life associated with the coexisting, severe, congenital heart disease. Clinical diagnosis in mature newborn infants and children seems to be possible as a result of the recently demonstrated significance of the presence of Heinz bodies in 10 per cent or more of the erythrocytes of the peripheral blood.

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## SPLEEN, SURGERY OF THE

M. Chaudhuri

Recent advances in haematology have greatly widened and improved the scope of surgery in the treatment of blood disorders. The indications for splenectomy today are more specific, based on better knowledge of physiological functions of this complex organ as well as of the other haemopoietic tissues. All the functions of the spleen are still not known, nevertheless, there are well recognised functions which have surgical significance as described by Whitby (1952), namely, its function as a blood reservoir, phagocytic action of its reticuloendothelial cells on effete or abnormal red cells, and its haemopoietic function which is chiefly marked in the foetal life. To this may be added its control over the activity of the bone marrow (Edwards, 1954). The concept of hypersplenism (Dameshek, 1953) has further broadened the



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field for surgical treatment. *It implies that there is physiological hyperactivity of the splenic functions, although unlike hyperthyroidism no specific histological changes in the structure of the organ occur as pointed out by Collen in his Moynihan lecture (1955). This however, helps in unravelling those pathological conditions which so far could not otherwise be explained, where splenomegaly due to unknown causes is associated with changes in the bone marrow and peripheral blood, and the condition is controlled only by splenectomy.*

Edwards (1955) in his presidential address to the Surgery Section of the Royal Society of Medicine emphasized that splenectomy is most effective in those conditions of hypersplenism where the bone marrow shows active haemopoiesis, or contains the precursor of those elements in which there is a deficiency in the circulating blood. He considers that there is a direct relation between the size of the spleen and the severity of the effects of hypersplenism; hence, better results of splenectomy are with bigger spleens. Dameshek (1957) also considers that only when the leucocyte and platelet counts are low that splenectomy is of value. Besides, for traumatic rupture, and occasionally for cysts, neoplasms or protozoal splenomegaly, splenectomy is now mainly done for specific types of blood dyscrasias as mentioned later.

Certain anatomical aspects are important from the point of view of surgery. Lately, the structure of the spleen and its vascular supply have attracted attention; the controversy over the nature of the vascular channels, whether closed or open systems, existed within the spleen has been clarified by Whipple (1954), who proved the existence of both the systems side by side. The presence of rich vascular network in the spleen has surgical significance, for it renders any trauma dangerous, owing to the risk of severe haemorrhage, and also indicates that during splenectomy the blood from the organ should be squeezed into the circulation before its removal. Lowdon (1955) points out the importance of the vascular supply to and from the hilum of the spleen by two mesenteries forming dorsal mesogastrium, since ligation of the splenic artery proximal to the origin of the left gastro-epiploic and short gastric arteries does not diminish the blood supply to the organ. This may have some bearing on the treatment of an aneurysm of the splenic artery. As Hill and Inglis (1955) consider that splenectomy is not always necessary if the spleen is normal, only excision of the aneurysm is sufficient since the blood supply to the organ is adequate through the vasa brevia.

Emergency splenectomy is vital for rupture of the spleen. Maingot (1952) observed that the rupture occurred in 30-40 per cent of all closed abdominal (non-penetrating) injuries with high mortality at 30 per cent. This is mainly due to delay in diagnosis and partly due to concomitant injury to the left kidney. He rightly emphasised that the so-called classical picture of internal haemorrhage is that of the final phase and treatment should not be delayed until these signs become apparent.

Although splenectomy is now mainly done for specific types of blood disorders, it also has its place in the treatment of splenomegaly even in the absence of hypersplenism simply as a palliative measure to relieve the patient of the heavy weight, as in very large spleens due to protozoal infection or idiopathic causes. Hutchison and his associates (1956) described their experience of splenectomy in 135 patients with Egyptian splenomegaly, 74 per cent of them were relieved and were able to return to full time work as agricultural labourers. Similar good results have been reported in cases of 'Tropical' or 'Bengal splenomegaly' by Chaudhuri, Saha, Basu (1956), its aetiology is not well known, probably follows repeated attacks of malaria. They consider that splenectomy is useful in those with evidence of hypersplenism affecting chiefly the neutrophils and platelets with symptoms of thrombocytopenia. Another interesting feature of these cases is that ultimately some of them present a picture of portal hypertension. Konar and Sen Gupta (1953) and Basu and associates (1955), recommend splenoportal venography before considering operation, by directly injecting into the spleen by percutaneous method. Chaudhuri, Basu and associates (1955) also recommend that in these cases splenectomy if done, should be combined with shunt operation. These workers found remarkable improvement following splenectomy, the blood picture returned to normal, although immediately after splenectomy there was leucocytosis. Sen, Sharad Kumar and Mangalik (1956) reported from similar findings in experimental rats that leucocytosis occurred following splenectomy, and also that there was no significant change in the leucocyte count following partial splenectomy, whether 50 or 70 per cent of the spleen was removed. Later they also reported that transplantation of splenic tissue in splenectomised rats restored the blood picture to normal irrespective of the amount of tissue that was transplanted. This has clinical implications since the presence of

accessory splenic tissue (Edward, 1955, Collier, 1955) or implantation during removal (Maingot, 1952) may cause recurrence of the disease as in idiopathic thrombocytopenia.

There are now definite indications for splenectomy in specific types of blood dyscrasias. All the authors advocate splenectomy as the method of treatment for congenital haemolytic anaemia and idiopathic thrombocytopenic purpura. Edwards (1955) considers that even in acquired type of haemolytic anaemia improvement occurs in 50 per cent of cases. The results of splenectomy are doubtful in Felty's Syndrome and in Cooley's anaemia. Although until recently splenectomy was not advised in myelosclerosis where the bone marrow is sclerosed and the spleen is supposed to have the haemopoietic function, but Aird (1957) and Edwards (1955) consider splenectomy useful in selected cases as the spleen also has destructive action on the red cells. The life span of the blood cells is made out by a radioactive tracer dose and if it is shortened, splenectomy is indicated.

Splenectomy is strongly recommended in familial type of congenital haemolytic anaemia with the red cells as spherocytes; these are more fragile and easily destroyed by the spleen. Frequently the condition is associated with acholuric jaundice and even gall stones and this requires exploration of the biliary tract. The condition is seen in infants and usually the operation is postponed until the age of 2 years or more, but Edwards (1955) reported excellent results of splenectomy on an infant 9 months old. Gross (1953) also reports excellent results under one year of age. Thrombocytopenic purpura must be of idiopathic type with diminished platelet count to have good results with splenectomy. Repeated platelet counts should be done following this operation as there is a tendency to a sharp rise in the platelets with a risk of thrombosis of the splenic vein or even of the portal system. Glenn and his associates (1954) report that in acute type of idiopathic thrombocytopenic anaemia spontaneous remission occurs frequently in children. Whereas results of splenectomy are good in chronic cases in adults, they are not so favourable in children and suggest that the conservative treatment should be tried before operation is considered. The modern view is that ACTH and cortisone should be administered if bleeding is persistent or severe to achieve remission, and splenectomy is considered if thrombocytopenia persists for 3-6 months. Collier (1955) also recommends cortisone therapy initially and splenectomy if relapse occurs.

Splenectomy is usually done through the abdominal approach by left paramedian, left oblique incision extending to the right rectus (Edwards, 1955) or by transverse incision; the latter is useful also for exploration of the biliary tract as in congenital haemolytic anaemia. Lately thoraco-abdominal approach, usually through the left 8th rib space, has become popular. This is of particular value in congestive splenomegaly with increased vascularity and adhesions between the organ and the diaphragm, as these can be dealt with easily under direct vision with less risk of haemorrhage from the splenic bed (Hart, 1953).

Splenectomy is being increasingly done incidental to other operations in this region as on the oesophagus, stomach and pancreas. A few cases of splenic vein thrombosis have been recorded following such procedures.

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## SPONDYLOSIS, CERVICAL

N. H. Wadia

Cervical spondylosis is now recognised to be one of the commonest causes of compression of the spinal cord or its roots. Changes in the cervical spine as seen in this condition, have been noted from time to time for more than 50 years, but under different names. Radiologically, it has been called osteophytosis, cervical osteoarthritis, spondylitis and various other names.

Osteoarthritis of the spine as a cause of compression of the spinal cord was discussed by Bailey and Cassamajor in 1911, with an account of 5 cases. A little later, the changes now described in cervical spondylosis were mistaken for chondromata arising from cervical intervertebral discs ; cord compression as a result of these was mentioned<sup>4, 11</sup>. Peet and Echols suggested that what were considered to be chondromata were really intervertebral disc protrusions<sup>10</sup>. It is only recently that the full pathology, pathogenesis, and neurological complications of the disease have been recognised and treatment suggested<sup>2, 3</sup>.

The term spondylosis implies a degenerative condition, and is meant to cover the changes that occur in the intervertebral discs and the resulting effect of these on the adjacent vertebrae and joints. Nosologically, strictly speaking, it should be distinguished from a "prolapsed intervertebral disc", if by prolapse is implied, a herniation of the nucleus pulposus through the annulus fibrosus. The primary change in spondylosis is a flattening and protrusion of the disc as a whole without nuclear herniation.

**Aetiology :** It is believed that spondylosis is a part of the natural process of aging, and is seen radiologically in 75 per cent of people above the age of 50, and 95 per cent above the age of 70 years. It is only in a few of these that obvious and striking neurological complications are seen, although Pallis et al<sup>9</sup> noted that careful neurological examination of people above 50 years without symptoms referable to this disease but showing radiological changes, showed abnormal physical signs suggesting slight involvement of the roots or cord in most cases.

In the series collected by Brain, Northfield and Wilkinson<sup>2</sup>, three-fifths of the patients were between 40-49 years when the symptoms began, the average age being 49 years. The part played by trauma to the neck was not clear—29 out of 45 patients of their series had no history of preceding trauma. In only 8 of these patients, a direct relationship was established. Males were affected twice as often as females, but perhaps more frequent trauma to the former may be the reason.

Congenital abnormalities of the cervical spine were noted in 4 of their patients and it has been suggested that the resulting disorder of mobility exerts an excessive strain on the normal adjacent joints and may therefore initiate spondylotic changes. Fig. 1 shows such an example from one of my patients.

**Pathogenesis :** This may be conveniently divided into two parts : (1) The changes in the vertebral column itself and (2) involvement of the central nervous system.

The primary change is one of dessication and dehydration in the affected intervertebral disc. The water content of the nucleus pulposus falls from 88 per cent at birth to 70 per cent in old age ; the high water content in the nucleus pulposus is due to it being made up of an amorphous mucoid material which has a high water-binding capacity<sup>12</sup>. With the process of aging, this mucoid material disintegrates, causing dehydration, loss of turgescence and flattening of the disc ; the whole disc or part of it protrudes backwards as a fibrocartilaginous bar or boss, which later undergoes calcification and even ossification. Reactive changes in the bodies of the adjacent vertebrae are stimulated by the protrusion, new bone formation and bony ridges appear above and below the protrusion. These are called osteophytes and may in their turn fuse with the disc protrusion. The collapse of the disc puts extra strain on the neuro-central joints because their alignment is disturbed, and secondary osteoarthritic changes with osteophyte formation take place—these are mostly in or around the intervertebral foramina. Occasionally, the osteophytic reaction may be started by a collapsed disc without actual backward protrusion. These changes may occur in any or all of the cervical discs, although it is

*PLATE XIX*

CERVICAL SPONDYLOSIS



Fig. 1

*Fusion of C5 and C6 vertebrae, with spondylotic changes at C4-5.*

PLATE XX

CERVICAL SPONDYLOSIS



Fig. 2

*Lateral view of the cervical spine showing narrowing of disc spaces anterior and posterior osteophytes and a well-marked lower cervical kyphosis (By courtesy of Dr. R. G. Ginde).*

Fig. 3

*This patient had clinical evidence of low cervical cord compression. Straight X-ray showed well-marked spondylotic changes at the appropriate level, making the diagnosis appear obvious.*

*Myelogram shows a slight indentation of the cord at C6-7 by a posterior osteophyte, and a complete block by tumour at C-7. At operation a large spinal meningioma was removed, and the patient made a complete recovery. Here therefore, the myelogram was the only way to clear a clinical misdiagnosis.*



believed (not on firm grounds), that they occur more often at C 5-6 and C 6-7 levels than elsewhere<sup>3</sup>. The osteophytes may be median, paramedian, dorsolateral or intraforaminal; often like a bar extending from one foramen to the other, right across the cord. Instability of the intervertebral joints allows excessive mobility of one vertebra on the other.

*The Nervous Complications* may be due to one or all of the following reasons :—

(a) Direct pressure on the cord or roots by the bony osteophytes. The nature and character of symptoms and signs depend on the exact sites of osteophytosis.

(b) Frykholm<sup>5</sup> studied in great detail the anatomy of the intervertebral foramen, in relation to the spinal root and its coverings. He pointed out that compression was not all due to the direct pressure of the prolapsed disc or the osteophyte, but is often the result of what he called, "root sleeve fibrosis". He maintained that as a result of constant rubbing of the root against an intraforaminal osteophyte or against the sharp margin of the pedicle (if the root is displaced backward), a reaction is set up in the coverings of the root, causing thickening, fibrosis, and hyalinisation of the dura and arachnoid, and a shrinking of these tissues causing a constriction and angulation of the root involved.

(c) Excessive forward and backward sliding of one vertebra on the other during neck movements would traumatise the cord repeatedly.

(d) Extension of the neck normally causes a protrusion of the ligamentum flavum into the spinal canal, and at the same time the cord moves forward; if this forward movement is prevented by an osteophyte, then the cord is squeezed in between the ligamentum flavum and the osteophyte everytime the neck is extended.

(e) The cord is tethered inside the spinal canal by the dentate ligaments; if the cord is displaced by an osteophyte then considerable stress is exerted on the cord at the points of attachment of these ligaments; the pyramidal tracts lie subadjacent in the cord and would suffer most damage under these circumstances.

(f) Ischaemia of the cord as a result of pressure on the anterior spinal artery or its branches by a median or a paramedian osteophyte is believed to play considerable part in damage to the cord<sup>7</sup>. Disturbed venous drainage also plays a part<sup>1</sup>.

*Symptomatology* : This is extremely varied depending on the end results of the various factors described above. It may be conveniently divided into three groups : (a) manifestations of the cervical spondylosis itself; (b) root symptoms; (c) cord symptoms.

(a) The presence of cervical spondylosis is suspected when a middle-aged or elderly patient complains of pain in the neck, especially on movement, and limitation of neck movements. When there is acute exacerbation of a chronic spondylosis, the pain may be so excruciating that practically no movements are possible and the neck is fixed in a position of torticollis. In the more chronic cases, as many as half of the patients may have no neck symptoms and the cervical spine movements may be free and painless; in the rest, there is limitation of movements of the neck in certain directions, especially in flexion, accompanied by pain and often crepitus and local tenderness.

(b) Root symptoms: These are far commoner than cord symptoms—they may be alone or along with the latter. The commonest symptom is one of root pain which in the acute cases may be of sudden onset and severe in character. It is always exacerbated by neck movements and may start suddenly after an accidental jerking of the neck. It may be localised to one root or several roots and accordingly the pain may be present selectively in one part of the arm, hand and fingers or in all of them. The more insidious symptoms of root irritation are tingling, sensation of pins and needles, occasionally burning or tearing sensation in the arm, and a generalised dull ache all over the limb. The symptoms are worse at night and tend to recur and remit from time to time. The patient may complain of localised or more generalised wasting and weakness in the affected limb after either mode of onset.

The physical signs mostly comprise of wasting, weakness and hypotonia in the muscles supplied by the affected root. Sensory impairment or occasionally hyperpathia within the distribution of the dermatome of the affected root, and diminished or lost reflexes mediated by the damaged spinal arch are noticed. The motor and sensory sides of the picture may not always be correspondingly severe.

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This is the picture in most cases but there are other modes of onset which need to be recognised.

1. Considerable wasting and weakness without sensory loss and few root symptoms.
2. Severe motor and sensory loss with total paralysis of the arm, considerable superficial and deep sensory disturbance and absent reflexes.
3. The only symptom primarily may be one of acroparaesthesia in one or both hands.
4. A spinal root supplies sensory fibres to muscles, ligaments and joints besides its cutaneous distribution—the former is often of a considerably wider area than the latter. This may cause the pain of posterior root compression to be spread over a much wider area than the one of cutaneous distribution. For this reason pain from cervical spondylosis has been confused for one of cardiac origin because the initial pain may be in the chest.

(c) *Cord Symptoms* : This condition is often termed as cervical myelopathy. It presents often with weakness in the lower limbs or one of the upper limbs. With the passage of time, the weakness increases and almost always involves all the four limbs although often asymmetrically. It often produces fairly severe handicap but rarely to the stage of making a patient bed-ridden. There is often localised wasting in the upper limbs. The tone in the lower limbs is increased and may be considerable at times. The picture in the upper limbs is a combination of upper and lower motor neurone involvement.

Root pains and paraesthesiae in the upper limbs are common. There may be tingling, numbness, burning or other sensory symptoms on the trunk or lower limbs if the long sensory tracts are involved. In two-thirds of all cases, superficial sensory loss or impairment is noted in the upper limbs ; on the trunk and lower limbs the loss is patchy and a clear-cut upper level is not often seen. Posterior column sensibility is not so floridly affected but postural errors and impairment of vibration of a mild degree are often seen in the lower limbs. Sudden forward flexion or extension of the neck may cause a "shock like" sensation down the spine, legs or arms.

Bladder involvement is often slight and at an advanced stage of the disease.

**Investigations.**—*Lumbar puncture* yields no useful information, as it rarely shows a manometric block or abnormal composition—occasionally the protein content may be raised to 100 mg per cent. It is often done to exclude a tumour.

**Radiology** : Cervical spine X-rays should be taken ideally in four positions—antero-posterior, lateral and two oblique. The radiological changes seen may be one of a combination of the following (Fig. 2) : (a) Narrowing of the intervertebral disc space. (b) Anterior and posterior osteophytes from the margins of the vertebrae adjacent to the disc. (c) Protrusion of the osteophytes into the intervertebral foramina seen in the oblique views. (d) obliteration of the normal cervical lordosis in acute cases or even slight kyphosis in very chronic ones. (e) There may be a spondylolisthesis and sliding of one vertebra on the other. This may be seen on straight lateral pictures but a considerable defect may be brought out on full flexion and extension pictures of the spine, when the ordinary lateral shows no striking changes.

**Myelography** : This is necessary to confirm the diagnosis, especially in doubtful cases or before operative treatment. It has been shown that considerable changes on straight X-rays may not be accompanied by cord or root compression as shown by myelography and a misdiagnosis made (Fig. 3). Again, slight changes in the straight X-rays may be accompanied by gross abnormalities in the myelogram. This is because the disc protrusion may have remained fibrocartilaginous, without any reactive osteophytosis and the former would not be seen on the straight X-rays.

**Prognosis** : After an initial downward course, the disease becomes stationary. The physical handicap may be great but it rarely endangers life. With proper and timely treatment, the prognosis is better.

**Treatment** : This is extremely difficult in chronic cases, and it is often not easy to make the correct choice of treatment amongst several alternatives.

**Conservative** : This is the initial treatment in all cases. In acute exacerbation of the disease, complete bed rest with neck immobilization and analgesics would give relief—it may have to be carried out for a few weeks. Neck traction has been reported of value in selected cases. When the excruciating pain has subsided in acute cases, or in chronic cases, a well moulded plastic, leather, or perspex collar is set round the neck to ensure maximum immobility with minimum discomfort. It may have to be worn for three to six months, and occasionally more if there is favourable progress or the neurological complications remain stationary. In cases which show improvement, the collar is taken off for gradually increasing periods, and selected neck exercises under the guidance of a trained physiotherapist are given. Results of conservative

treatment have not been worked out in a large enough series but Brain et al<sup>2</sup> claim improvement in 50 per cent of their patients by these methods, although practically, no patient returned back to normal. In a large number of cases, it prevents or slows down further deterioration.

**Operative :** Operation is undertaken only if the conservative treatment has failed or the compression is acute, the pain unbearable, and if there is rapid deterioration in the neurological signs. For intraforaminal osteophytes pressing on the roots, a direct attack is possible and gives fairly good results. Removal of median and paramedian osteophytes lying in front of the cord becomes a hazardous and highly technical surgical procedure. So in cord myelopathy, the operation is one of simple laminectomy with or without division of the dentate ligaments. This operation allows the cord to move backwards easily. If there is sliding of one vertebra on the other, then spinal fusion needs to be done.

Considerable relief is noted in 60 to 65 per cent of patients undergoing operation for the root compression<sup>6</sup>. In the cord myelopathy cases, Northfield has a fairly large series treated by laminectomy. In this series of 38 cases, 13 showed considerable improvement and 9 slight improvement<sup>8</sup>.

### Conclusions

Spondylotic changes in the cervical spine are seen in a great many individuals above 60 years of age. Evident or gross neurological involvement is seen only in a few. Whilst this forms one of the commonest group of central nervous system diseases according to the Western literature, no worthwhile study has been made of it in India.

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### SPRUE, TREATMENT OF

R. Subramaniam

Sprue was considered as a worldwide problem although limited largely to overcrowded, underdeveloped tropical and sub-tropical areas. It has been felt that many millions of people live in these areas in a little above a state of starvation and in addition they act as hosts for a variety of parasites, unicellular organisms such as *E. histolytica* or, multicellular parasites as ankylostome. Many of them give rise to chronic intestinal disturbances which in course of time may fulfil the criteria of what is called "sprue". It was felt that the best way to handle it is to prevent it and this is being done in places where funds are available.

The diagnosis is all important and proper treatment for the tropical sprue is associated with an understanding of the syndrome. In the initial phase, the disease is associated with impaired gastro-intestinal absorption of foodstuffs, vitamins and minerals. This alteration leads to progressive nutritional deficiency, reflected clinically in later stages by the presence of a megaloblastic bone marrow, anaemia and glossitis. However tropical sprue may occur without macrocytic anaemia or tongue changes. Natives of tropical areas with existing dietary deficiencies may manifest the complications of avitaminosis quickly to emphasize the speed with which the defective small bowel absorption may be associated with the more classic signs and symptoms of deficiency of specific nutritional agents. In the early phase the symptoms are of fatigue, lassitude, anorexia and vomiting. Sprue should be considered a syndrome rather than a specific disease, in which the body is affected, and not merely as affecting alimentary tract or the haemo-



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poietic system. In the treatment, one should take note of the precipitating and predisposing factors and associated diseases. The diagnosis of sprue is made difficult in that patients with nutritional macrocytic anaemia and idiopathic steatorrhoea, may have similar presenting symptoms. In these the patients may have bulky liquid stools associated with abdominal distension, severe pain and loss of weight. Glossitis and macrocytic anaemia may frequently be present; in nutritional macrocytic anaemia the stools are brownish in colour and watery rather than yellow or whitish yellow in colour as they are in sprue. Idiopathic steatorrhoea apparently is a primary defect resulting in part in failure of certain digestive enzymes. In nutritional macrocytic anaemia and sprue the enzymes tend to be more normal but there is considerable disturbance in absorption for one reason or another. The tropical and nutritional macrocytic anaemias respond dramatically to treatment with folic acid but idiopathic steatorrhoea is always difficult to treat and frequently ends fatally. Sprue should be considered as a deficiency disease but the role folic acid, vitamin B<sub>12</sub> and probably other factors involved, is not clearly understood. As a result of these deficiencies intestinal absorption is impaired resulting in poor absorption of vitamin B complex factors, iron and other minerals, fat soluble vitamins and proteins.

Complete cure can be achieved by the administration of folic acid, vitamin B<sub>12</sub> or liver extract. When there is a neurological disturbance vitamin B<sub>12</sub> or liver extract is preferable to folic acid. Even in such cases, folic acid can be used provided vitamin B<sub>12</sub> supplement can be given. The results are better in younger persons and where the disease is treated earlier. Treatment can be divided into two headings, viz. drug therapy which is specific and adjuvant measures.

Drug therapy consists in the use of folic acid, vitamin B<sub>12</sub> or liver extract. The results are dramatic. Diarrhoea first ceases and the blood picture reverses to normal and rapid regeneration of haemoglobin takes place. The bone marrow which was megaloblastic becomes normoblastic. Folic acid may be administered orally even in cases of diarrhoea. 15 to 20 mg in tablet form is suggested as the initial dose. It may be given parenterally if desired. This is maintained till the reticulocytes reach a peak say for two weeks and after that the dose can be reduced to 10 to 15 mg and maintained at this level until the blood levels are normal and all the symptoms have disappeared. The maintenance dose is 2.5 to 5.0 mg orally and may be continued for some weeks.

Vitamin B<sub>12</sub>—15 mg administered parenterally daily for two weeks is quite sufficient, thereafter, every other day for two weeks or until the blood picture returns to normal. This is followed by 15 µg once in two weeks. This prevents relapses. If vitamin B<sub>12</sub> is administered orally very large doses are required.

Liver extract—For liver extract to be effective it should contain 15 U.S.P. units per c.cm, or 15 mg of B<sub>12</sub> per c.cm; 15 units of purified extract should be administered parenterally daily for two weeks and then every other day for two additional weeks. By this time the blood is expected to reach a maintenance dose. In elderly or severely ill patients 15 units a week is required as a maintenance dose.

Adjuvant measures: These are (1) *diet*: The diet should be high in protein, low in carbohydrate and very low in fats. Fat restriction is particularly recommended for patients with marked bowel disturbance.

(2) *Rest*: In severely ill patients rest is essential but it becomes unnecessary to recommend it since they are already confined to bed.

(3) *Steroids*: Adrenal steroids and corticotrophin are useful in the treatment of tropical sprue. They have no advantage over folic acid. They give a sense of well-being and are useful in the stubborn cases as an adjuvant.

Complications: The over-all response to folic acid and vitamin B<sub>12</sub> is far more dramatic than it is with steroids.

The effect of administration of steroid compounds is that the weakness disappears. Diarrhoea decreases in severity and the blood regenerates quicker. It was felt that supplementing the diet with B complex factors, vitamins A, D, and K, calcium and iron and other nutrients which are lacking in these patients is necessary. In the early stages probably adequate diet alone may improve the patient's condition. To prevent relapses folic acid therapy should be maintained.

### REFERENCE

Guillermo Garcia. Lopez, Frank Gardner, Tom D.  
Spies and Richard W. Vilter: *Blood*, Vol. XI  
No. 6, June '56, page 76.

**SQUINT, SURGICAL TREATMENT OF***H.D. Dastoor*

The treatment of squint, particularly surgical, is both fascinating and at the same time complicated. Correction of physical disfigurement gratifies the surgeon and the patient alike ; but the relative uncertainty of its ultimate results subscribes to the complexity in the line of treatment. The correction of such a disfigurement is most essential in a child before the school-going age as otherwise it leads to psychological retardation and feelings of inferiority complex in the child. The successful treatment of squint involves two modes of correction, viz. the physical correction by maintaining the straight alignment of the two eyes with their correlated normal movements, as well as the physiological correction in acquiring the normal binocular vision with stereopsis. The surgical interference when carried out during early childhood not only corrects the physical defect but is of great help in the accomplishment of physiological correction of the squinting eye, by correction of the refractive error, occlusion to improve the amblyopia, and exercising with orthoptics. The correction of refractive error alone may remove the squint, especially in the accommodative type of strabismus, but in other cases if the non-surgical line of treatment fails to correct the squinting eye, then surgical intervention is essential at the earliest stage, in order to correct not only the physical defect but to promote the correction of its physiologic aspect. The earlier the onset of squint in infantile and congenital cases, the greater is the necessity to operate early as the nervous mechanism in an infant is then pliable to establish binocular vision and later on stereopsis in those eyes that are straightened surgically. Surgery can reset the eyes in alignment at any age, even in elderly patients, for cosmetic purpose.

The surgical treatment of squint is mostly done for concomitant variety and occasionally for the paralytic and the latent types. As aforesaid this type of surgery is full of complexity because the end results are variable not only in the hands of different surgeons with the same type of operation, but also in the hands of the same surgeon with the same type of operation performed on different patients. It requires finer judgment acquired by practical experience as regards the precision in this type of surgery. The usual trend is to rectify the squint in stages by correcting the residual deviation by repeated surgery. Hence it is most desirable to inform the patient or the parents of the possible requirement of repeated surgery for full correction of the squinting eye, in order to avoid subsequent feeling of disappointment. The amount of correction of the deviation is dependent upon several factors, the important amongst them being, the age of the patient, the duration and the degree of the squint, the strength of the muscles involved, the element of paresis in the muscle and the prominence of the eyeball. The younger the age of the child, the greater is the effect of the operation. The shorter the duration of the squint, the greater is the effect of the operation. The larger and more variable the angle of deviation, the greater the effect of the operation. The stronger the muscle that is operated upon, the greater is the effect on it of a strengthening operation and the less is the effect of a weakening operation. An element of paresis in the muscle lessens the effects of the operation. The effects of the operation are greater on large and prominent eyes and less on small deep-seated eyes.

The general principle in squint surgery is to weaken or lengthen the overacting stronger muscle and to strengthen or shorten the underacting weaker muscle. Amongst the operations to weaken the action is tenotomy and tenoplasty or recession. Amongst the operations to strengthen the action is reefing or tendon tucking, resection and the advancement operations. Though no mathematical calculations serve exactitudes as previously mentioned, yet a rough guide would be that one mm of advancement or recession will correct upto 4 degrees in the medial rectus and 2 degrees in the lateral rectus. In infants it is better to under-correct by 10 degrees because this residual squint disappears under orthoptic treatment ; whereas in elderly patients it is better to over-correct by 10 degrees.

Tenotomy is done as "complete" or "free tenotomy" where the tendon is divided close to its scleral attachment, taking care not to sever its adjacent fascial expansions extending to the adjacent extraocular muscles and to the covering conjunctiva. The muscle there recedes backwards by 5 to 7 mm and gets adherent in that area. Free tenotomy is usually preferred for the lateral rectus. For the medial rectus a recession is usually preferred. In a "guarded" tenotomy the tendon at its insertion is cut but it is prevented from retracting farther backwards for more than 5 to 6 mm by inserting sutures between the muscle end and the stump of the insertion leaving a gap between the two. In tenoplasty, otherwise known as "partial teno-

## Squint, Surgical Treatment of

tomy" or "marginal myotomy" as done by Harman's, the tendon is lengthened by making a series of cuts at right angles into the margins of the muscle and its tendon, thereby extending and stretching it like a parallel ruler. The lengthening gives 5 degrees of correction. This technique is usually employed for the correction of small degrees of vertical displacement in hyperphoria by making two cuts only, one from each edge of the tendon, two-thirds across. The cut nearest the cornea determines the direction of the movement. This cut made from above lowers the eye. In "recession" the tendon is cut at its insertion and is separated from its lateral expansions and superficial attachments and the cut end of the tendon is reattached to the sclera farther backwards for not more than 5 mm in children and 7 mm in adults for an internal rectus, and by 2 mm more if needed in case of an external rectus. A 5 mm recession corrects approximately from 6 to 12 degrees of convergent deviation. Recession of the superior or inferior rectus must be done with great care to make the new insertion exactly parallel to the old one in order to avoid a torsional displacement. It is therefore preferable to operate on the elevator muscles and avoid the depressors whose accurate balance is necessary for reading and walking. A retroplacement by 3 mm corrects almost 10 degrees of deviation.

"Reefing" or "tendon tucking" is done to shorten the muscle. In the O'Conner Cinch technique the muscle tendon is split as far as its transition into muscle, into four strands and winding sutures are passed around these strands, which when tightened shorten the length of the tendon. Similar effect is achieved by the Horman's reefing or tucking technique where the tendon is folded and tucked in by inserting sutures and thereby producing plication of the tendon. Special tendon tucking forceps may be used to secure it. This technique corrects from 5 to 10 degrees of deviation. In the "resection" operation the muscle is shortened by cutting away a portion of its distal end, and the cut muscle end is resutured to the original stump of insertion. A resection of the lateral rectus by 7 mm can correct a deviation of about 10 degrees and that by 10 mm can correct to about 18 degrees. Resection of the lateral rectus is usually done in conjunction with a recession of the opposing medial rectus; and hence recession of 5 mm of medial rectus when combined with resection of 7 mm of lateral rectus usually corrects a deviation of 15 to 25 degrees. In "advancement" operation the muscle tendon is similarly exposed and cut, and this end is resutured farther forwards towards the limbal end of the sclera. This gives a greater effect of correction and hence is suitable in squints of extreme deviations.

In the surgery of oblique muscles "myotomy", "myectomy" or "myomectomy" is done on the inferior oblique muscle when there is an updrift of the affected eye when the gaze is directed nasally towards the opposite side. This may be due to paresis of the ipsilateral superior oblique or paresis of the contralateral superior rectus. The operation is done for the relief of ocular torticollis. The muscle may be approached through a lower lid skin incision near the inner side of the inferior orbital margin, or transconjunctivally with the lower lid everted (Chavasse's operation). The muscle is cut preferably with an electric cautery (myotomy); or only a portion of it is removed (myectomy, myomectomy). The inferior oblique can also be "recessed" from its original insertion. When shortening or strengthening of this muscle or of the superior oblique is desired a reefing or tucking or resection may be performed on it. The superior oblique can be weakened or lengthened by a tenotomy or tenectomy operation in cases where marked down-drift of the eye occurs whenever the gaze is directed towards the opposite side. This may be due to paralysis of the ipsilateral inferior oblique or of the contralateral inferior rectus. The muscle is approached by incising the upper conjunctiva and retracting laterally the superior rectus under which passes obliquely the tendon of the superior oblique.

Operations for corrections of paralytic squint are done on the same principles as for concomitant variety. They are done after fully ascertaining that the paresis is incurable and the squint has been present for almost a year. The resulting effect of the operation is less effective than the same one performed on concomitant (non-paralytic) squint. A "muscle transplant" operation is also done for achieving better motility of action in cases of lateral rectus paralysis from lesions of the sixth nerve. In this, strips from the outer or sometimes the inner sides of the superior and the inferior recti are transplanted in the paralysed (lateral) rectus.

### REFERENCES

1. Epstein, G. J.: Strabismus, Lea and Febiger, Philadelphia, U. S. A.
2. Lyle, T. K., and Jackson.: Practical Orthopetics in the Treatment of Squint, H. K. Lewis, London.

PLATE XXI

SURGICAL TREATMENT OF SQUINT



*A case of right eye, convergent concomitant strabismus operated by recession of the right medial rectus combined with resection of the right lateral rectus.*



*A case of left eye, divergent concomitant strabismus, operated by tenotomy of the left lateral rectus combined with advancement of the left medial rectus.*



3. Kramer, M. E.: Clinical Orthoptics, C. V. Mosby and Co., U. S. A.
4. Spaeth, E. B.: The Principles and Practice of Ophthalmic Surgery, Lea and Febiger. Philadelphia, U. S. A.
5. Philips A. S.: Ophthalmic Operations, B. T. and Cox., London.

## STERILITY

K. Bhasker Rao

In about 60 per cent of all cases of sterility tubal blockade is found. The commonest site of tubal block is at the medial end of the tubes, rest of the tube with the "egg-catching" fimbriae remaining normal. This condition is believed to result from mild subclinical catarrhal inflammation following a normal labour or abortion. Operations on the tube to restore the patency are done after the husband is found fertile and after the tubes have been found blocked by tubal insufflation tests done twice (after giving an antispasmodic) and after location of the block by uterotubogram. Genital tuberculosis must always be ruled out in these cases. Best results are obtained with salpingolysis but with salpingostomy (especially after hydrosalpinx) or tubal implantation operations, results are not so good, but the outlook on the whole is 3 times better now than what it was 20 years ago when Greenhill presented his first paper on this subject. In over 2000 tubal plastic operations done by different surgeons the pregnancy rate has been on an average about 20 per cent and the ectopic rate about 15 per cent. But the live birth rate is also about 15 per cent. Greenhill<sup>1</sup> recommends better and more careful choice of cases for tuboplasty and hopes that at least 50 per cent pregnancy rate may be achieved in these cases. Hellman<sup>2</sup> and Johnstone<sup>3</sup> have both described their techniques in detail and given their results.

In cases of sterility, artificial insemination may be indicated under certain circumstances, either from the husband (A. I. H) or from a donor (A. I. D.). The genetic and legal implications have been stressed by 2 writers<sup>4,5</sup> recently. Though it may be indicated medically, still the written consent of the parties involved is taken and a healthy but unknown donor is selected. However, the questions of illegitimacy, adultery and inheritance which still arise, are not yet settled. There is also a risk of the biological father being sued, the definition of adultery being not easy. In the U. S. A., one court considered a child born after artificial insemination as legitimate whereas another held such a child to be illegitimate. All parties involved in A. I. D., may be exposed to legal action and the matter becomes more complicated by the practice of mixing husband's semen with donor's before insemination.

## REFERENCES

1. Greenhill, J. P.: *Amer. J. Obstet. Gynaec.*, 72:, 516, 1956.
2. Hellman, L. M.: *J. Obstet. Gynaec. Br. Emp.*, 63 : 852, 1956.
3. Johnstone, J. W.: *J. Obstet. Gynaec. Br. Emp.*, 62 : 410, 1955.
4. Hollaway, A. D.: *Obstet. and Gynaec.*, 7 : 621, 1956.
5. Pommeranke : *Obstet. and Gynaec.*, 9 : 187, 1957.

**STERIOD, HORMONES—See HORMONES, STERIOD**

**STIMULANTS OF THE CENTRAL NERVOUS SYSTEM—See CENTRAL NERVOUS SYSTEM, STIMULANTS OF**

**STOMACH AND SMALL INTESTINE, SURGICAL ASPECTS OF THE DISEASES OF**

S. M. Nawab

## Peptic Ulcer as a Surgical Problem

Ogilvie reports that 10 per cent of adults in Great Britain suffer from peptic ulceration. The cause lies in the stress of modern life with overaction of the autonomic nervous system and the "hormonic system". Injury to the mucosa, due in India to the excessive use of spices and condiments is another cause and the fixity of the mucosa in the region of the lesser curvature of the stomach and the first part of the duodenum is the third important factor in the aetiology of peptic ulceration.

The role of hydrochloric acid in the stomach is thoroughly discussed. In ulcer patients this is secreted at an abnormally high level and even when it is not needed for the digestive processes.

**Indications for Surgery :** (a) Gastric ulcer (1) of doubtful innocence—e.g., those ulcer, occurring in persons over 45 years, (2) ulcers of the pylorus or on the greater curvatures

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- (3) ulcers over an inch in diameter or associated with achlorhydria or hypochlorhydria,
- (4) gastric ulcers not healed after one year of medical treatment.

(b) Duodenal ulcer: (1) three very important indications for surgery are stated, viz. perforation, stenosis or haemorrhage of 2 pints or more in persons over 50 years. (2) failure of medical treatment carried out for a reasonable period.

The author recommends the "law of ten", i.e., when the patient has lost more than 10 per cent of weight or 10 per cent of his working time and the "law of forty" i.e., when he has reached the age of 40 and has yet an active peptic ulcer.

The operation advised is partial gastrectomy, which has a mortality of about 1 per cent and a cure rate of at least 90 per cent. The author lays stress on removal of the whole pyloric mucous membrane and the body of the stomach and points out that the size of the stomach should be no longer than the diameter of the small intestine into which it empties.

### **REFERENCE**

Ogilvie, Sir Heneage : *Lancet*, 244 : 555, (1952).

## **Incidence and Predisposing Factors in the Aetiology of Peptic Ulcer**

Avery Jones points out that by the time individuals reach the age of 45-54, one in ten has peptic ulcer and 1 in 40 has severe pain and troublesome complications. Between 1938 and 1955 the incidence of acute duodenal perforation had been doubled, largely as the result of increased incidence of duodenal ulceration.

The author discusses on environmental factors, geographical incidence, occupational relationship, constitutional factors, and the age and sex incidence of peptic ulcer cases. Amongst patients with duodenal ulcer there is a high incidence of the blood group O. This may be due to a diminished secretion (or absence of secretion) of specific mucopolysaccharide in the saliva which in some way protects the gastric mucosa in other blood groups.

### **REFERENCE**

Jones, Avery F. : *B.M.J.*, 1 : 719, (1957).

## **Surgical Management of Uncomplicated Duodenal Ulcer**

The three main operative procedures carried out for the treatment of duodenal ulcer are reviewed by Capper.

1. *Gastro-enterostomy* : The author holds that from a study of a large number of cases it is proved that 30-40 per cent will have recurrent ulcer after gastro-enterostomy, while 72 per cent may have complete relief after the operation ; 22 per cent at least are worse off 10 years after the operation.

2. *Vagotomy* : The recurrence rate was 27 per cent after vagotomy done alone in 4076 cases.

3. *Vagotomy with gastro-enterostomy* : The author observes that this combined operation has nearly a 10 per cent recurrence rate after a 5-year period of observation.

4. *Poly-gastrectomy* : This measure is estimated to be accompanied by a recurrence rate of 2.4 per cent (observations of 1489 cases). The incidence of dumping syndrome of a mild to severe degree is held to be about 8 per cent.

### **REFERENCE**

Capper, W. M. : *Proc. Royal. Society Med.*, 49 : 501 (1956).

## **Late Results of Vagotomy with Gastro-jejunostomy or Pyloroplasty in the Treatment of Duodenal Ulcer**

Davies reports on a study of 366 cases and observes a recurrence rate of 5.6 per cent for gastro-jejunostomy and 4.5 for pyloroplasty. With the former procedure satisfactory results were obtained in 92.4 per cent and with the latter in 87.9 per cent. There was no gastric retention in the former case while it was 6 per cent in the latter. The operative mortality was 1.5 per cent in both groups.

The author concludes that the increased recurrence rates preclude a more frequent adoption of these operative procedures.

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It is, however, claimed that these operations should be selected where it is essential that the post-operative caloric intake may be high as in heavy manual workers or in cases with pulmonary tuberculosis.

### REFERENCE

Davies, Lloyd, J. A. : *B.M.J.*, 2 : 1086 (1956).

### Management of Anastomotic Ulcer

Blint and Cooper review the results of treatment of 160 patients with anastomotic ulcer following gastro-jejunostomy or partial gastrectomy. For the former partial gastrectomy with vagotomy is recommended as the treatment of choice. For anastomotic ulcers which follow partial gastrectomy, vagotomy with or without a limited gastric resection to remove the ulcer is recommended.

Total gastrectomy as a final step is suggested for those cases who show persistently recurring anastomotic ulcers.

### REFERENCE

Blint, J. A., Cooper, G. W., et al. : *Lancet*, II : 551, (Sept. '57).

### Bad Gastrectomies

Kinsella, reviewing the history of partial gastrectomy in Great Britain and on the Continent of Europe, points out the stages through which this form of radical surgery won its place; he quotes Ogilvie that "the bad results of gastrectomies are the results of bad gastrectomies". The commonest fault consists in an improper placement of the afferent loop resulting in dumping syndrome.

The author warns against substitute operations aiming at conserving the ulcer tissue. These are based upon an inadequate conception of the pathology of ulcer and would in course of time result in a large crop of recurrence and other complications.

### REFERENCE

Kinsella, V. J. : *B.M.J.*, 2 : 1277 (Dec. 1956).

### Vagotomy with Gastro-jejunostomy in the Treatment of Chronic Duodenal Ulcer

Sen and Das Gupta comment on the results of 41 cases who were undernourished, underweight and unfit for gastrectomy. There was no mortality in their series and a satisfactory result is reported by them in 94 per cent of cases. The authors advocate this operation in feeble and undernourished patients unfit for gastrectomy.

### REFERENCE

Sen, A. K. and Das Gupta, T. : *Jr. Indian Med. Assoc.*, 27 : 84 (1956).

### Post-gastrectomy Syndrome

Two hundred and twenty-one patients are reviewed who had gastric resection, gastro-enterostomy or vagotomy. Excellent results are reported in 52.8 per cent, fair in 27.4 per cent, poor in 9.8 per cent. Mild to moderate dumping occurred in 54 patients of the group with fair results and 5 patients belonging to the group had poor response. Some of the rare sequelae such as weight loss, anaemia, neurasthenia, recurrent ulcer, marginal ulcer, haemorrhage, cancer of the stomach, regurgitation of bile and diarrhoea or constipation, are described. Gastric resection is concluded as the operation of choice to relieve ulcer symptoms of long duration.

### REFERENCE

Lassen, H. E. : *Acta. Med. Scandinav.*, 155 : 475-483 (1956).

### Toxic and Nutritional Disturbances of the Small Intestine Associated with Surgery of the Gastro-intestinal Tract

1. *Diarrhoea after Gastrectomy*: Reduced gastric acidity with bacterial proliferation in the upper jejunum is considered as the most important factor.

2. *Post-operative Necrosis of Intestinal Mucous Membrane*: Twelve cases are reported by Bruce. Cholera-like diarrhoea occurs abruptly with rapid collapse and circulatory failure



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often resulting fatally within 48 to 72 hours. There is extensive necrosis of the mucosa of the jejunum, the ileum, the colon or of all the three structures. Intense vasoconstriction of intestinal vessel from shock is considered by the author to be a likely cause.

Other disturbances listed by Bruce are as follows :

3. *Small Bowel Obstruction*
  - (i) Paralytic ileus,
  - (ii) Toxic (peritonitic) ileus,
  - (iii) Mucosal oedema of jejunum after gastrectomy.
4. *Disorders of Digestion and Absorption*
  - (i) Jejunio-ileal insufficiency following extensive resection of gut,
  - (ii) Blind loop or *cul-de-sac* syndrome,
  - (iii) Chronic intestinal hurry
    - (a) following gastrectomy, or
    - (b) following gastro-jejuno-colic fistulae.
5. Loss of digestive juices from biliary, pancreatic or intestinal fistulae.

### **REFERENCE**

Bruce, J. : *Proc. Royal Society Med.*, 48 : 245 (1956).

## **Evaluation of the Use of a Segment of Jejunum to Replace the Stomach Following Total Gastrectomy**

In 25 patients after total gastrectomy a segment of jejunum was utilised to restore continuity between the oesophagus and the duodenum. Three patients died and 11 had complications but in the remaining 10 the jejunal loop functioned satisfactorily. The authors claim that this technique prevents oesophagitis and the regurgitation of upper gastro-intestinal secretions ; it also provides for these patients for a satisfactory nutritional status post-operatively.

### **REFERENCE**

Free, E. A., Mannex, M. Jr. and Leals, J. M. :  
*Ann. Surgery*, 144 : 94-949 (1956).

## **Management of Bleeding Gastro-duodenal Ulcer**

Writs et al review the treatment of bleeding ulcer and draw attention to the following observations :

1. Mulengracht (1940), reported a mortality of 2.5 per cent in a large series of bleeding peptic ulcers treated medically by an early feeding regime.
2. Rasberry and Millar (1943), reported 4 per cent mortality under medical treatment.
3. Finisterer (1936) and Gordon Taylor (1937) had long advocated surgical treatment for bleeding peptic ulcer.
4. Stewart (1952) recommended that all patients with massive bleeding should have immediate surgery and reported a mortality of 10.7 per cent in this group.

The authors point out the necessity of a " bleeding team " being available to act in an advisory capacity. While all patients should at first have an initial trial on medical management those who continue to bleed should be immediately considered for prompt surgical intervention.

### **REFERENCE**

Writs, Welmore C. and Brodi, T. : *J.A.M.A.*, 163 : 1229 (1957).

## **Early Diagnosis in Massive Upper Gastro-intestinal Bleeding**

The author reports that 70 per cent of these haemorrhages are due to peptic ulcer of the stomach and duodenum, 10-15 per cent to oesophageal varices, use of aspirin and of cortisone and other steroids. Phenylbutazone used for the treatment of rheumatic diseases and reserpine for hypertension are also important agents provoking gastro-intestinal haemorrhage. Lastly, hepatic cirrhosis should always be excluded in a case of haematemesis.

### **REFERENCE**

Brock, I. V. : *J.A.M.A.*, 163 : 1217 (1957).

## **Bleeding Haemangiomatous Hamartoma of the Small Bowel**

Robinson and his co-workers discuss the aetiology of massive gastro-intestinal bleeding. Apart from gastric and duodenal ulcer, a persistent Meckel's diverticulum and haemangiomas

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are possible sites of bleeding. Haemangiomas form 0.3 per cent of all gastro-intestinal tumours and 3.4 per cent of all tumours of the small intestine.

Associated haemangiomatous lesions on the skin and on the visible mucous membrane may assist the diagnosis in some cases.

These vascular lesions are developmental anomalies and not true neoplasms.

### **REFERENCE**

Robinson, A. F., et al. : *B.M.J.*, 1 : 990 (1957).

## **The Physiological Mechanism of Death in Massively Bleeding Peptic Ulcer**

Harry Le et al conducted experiments on dogs in whom cannulae were introduced in the femoral and gastroduodenal arteries, and compared the results of experimentally induced bleeding from these vessels.

They conclude that fatal results of massive bleeding from the gastroduodenal artery in chronic duodenal ulcer is due to severe anoxia in the liver resulting from fall in hepatic arterial pressure and blood flow. Reflex spasm of the hepatic artery soon occurs and long continued hepatic anoxia results in irreversible liver damage which can only be controlled by urgent surgery and massive transfusion.

Penicillin and other antibiotics are good prophylactic agents against hepatic infection and should always be administered.

General anaesthetics produce extensive hepatic necrosis in anoxic liver. Local, regional or spinal anaesthesia should therefore always be preferred.

### **REFERENCE**

Le, Harry, H. Veen, A. G., Mulder, et al. : *S.G.O.*, 94 : 433 (1952).

## **Emergency Gastrectomy as a Preferred Mode of Therapy for Perforated Gastro-duodenal Ulcer**

Out of 38 patients with perforated duodenal ulcer, 15 were subjected to primary gastrectomy without mortality while 5 of the 18 patients treated with simple closure died. The author supports the principle of primary gastrectomy for perforated gastro-duodenal ulcer in suitable patients.

### **REFERENCE**

Allen, F. R. : *J. Nat. M. A.*, 48 : 384 : 388 (1956).

## **Excretory Function of the Stomach and Treatment of Uraemia in Cholera by Gastric Lavage**

Lahiri et al report on 11 cases of uraemia after cholera who were treated with gastric lavage with 10 per cent sucrose solution. Nine were cured and 2 died. The author holds that the stomach has an excretory function and that nitrogen is excreted in measurable amounts with the gastric secretion. This excretion occurs both in health and disease and that gastric lavage with hypertonic solution further helps such gastric excretion of nitrogen.

### **REFERENCE**

Lahiri, S. C. and Basu, S. N., et al. : *Journal of Indian Medical Association*, Vol. 27 : 345 (Nov. 1956).

## **Volvulus of the Stomach**

Sinha reviews 150 previous cases of volvulus of the stomach and reports 2 cases under his own observation.

1. A 21 years old male in whom a preoperative radiological diagnosis was made. At operation the stomach which had undergone one complete twist in the anticlockwise direction was filling up the entire abdominal cavity, from the epigastrium to the pelvis. After reduction of the volvulus the patient had an uneventful recovery.

2. A 60 years old male patient who was in the habit of swallowing 3 to 5 yards of cloth as a *yogic* feat developed symptoms of acute abdomen soon after one such feat. At laparotomy an organo-axial volvulus was reduced.

### **REFERENCE**

Sinha, R. V. P. : *Indian Journal of Surgery*, 15 : 104 (1953).

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### **Early Diagnosis of Carcinoma of the Stomach**

Myers has analysed the histories of 106 patients with gastric carcinoma. The mortality rate for carcinoma of the stomach has decreased a little in the U.S.A. during the last 50 years and the author makes a plea for an early diagnosis. The main reason for the high mortality is the failure of the patients and their physicians in taking a serious view of the early symptoms of carcinoma of the stomach, such as loss of appetite, indigestion and flatulence of some duration.

#### **REFERENCE**

Myers, Hu. C. : *J.A.M.A.*, 163 : 159 (1957).

### **Primary Malignant Neoplasms of the Duodenum**

Seventeen cases of primary malignant duodenal tumours are reported—14 adenocarcinomas and two sarcomas. Three types are described :

1. Suprapapillary with symptoms of pyloric obstruction ;
2. Peripapillary with obstructive jaundice ;
3. Infrapapillary with gastro-intestinal haemorrhage.

X-ray studies are very valuable. Treatment consists of prompt surgical exploration and excision or a palliative procedure if the former is not technically feasible.

#### **REFERENCE**

Ochsner, S. and Kleckner, Martin S. : *J.A.M.A.*, 163 : 413 (Feb. '57).

### **Metastases of Carcinoid Tumours**

Standeven reports on his 2 patients who had several carcinoid tumours in the ileum with a large secondary deposit in the left lobe of the liver. Diagnosis was made from (1) *Clinical features* : periodic flushing of the skin with burning sensation and rise of temperature with cyanosis, bronchospasm, pulmonary stenosis with a harsh systolic murmur, diarrhoea, palpable tumour in the abdomen with an enlarged liver containing metastatic growths ; (2) estimation of 5-hydroxytryptamine in the blood and 5-hydroxyindole acetic acid in the urine.

Treatment consists in removal of the tumour and as many metastases as possible. The relatively benign nature of the tumour justifies radical surgery.

#### **REFERENCE**

Standeven, A. : *Post-Graduate Md. Jr.*, 33 : 175, (1957).

### **Surgery in the Treatment of Abdominal Tuberculosis**

Misra discusses in detail the surgical management of tuberculous stricture of the ileum.

Where the lesion is mainly above the ileo-caecal valve a one-stage right hemicolectomy is recommended. For lesions higher up in the ileum, up to 20 in. of the ileum can be included in the resection. Where multiple strictures in the ileum are present, multiple anastomoses are preferred to extensive resection. The value of adequate blood transfusion and chemotherapy are stressed by the author.

#### **REFERENCE**

Misra, S. C. : *Jr. of Indian Med. Assoc.*, 23 : 240 (1954).

### **Volvulus**

Anderson reviews 160 cases of intestinal obstruction of which 20 per cent were due to volvulus of the small intestine, caecum or the sigmoid colon. Three different types of these volvulus of the small intestine occurred in 34 per cent of cases and had an operative mortality of 57 per cent whereas volvulus of the sigmoid had a mortality of only 20 per cent.

The tightness of the twist at the base of the mesentery with early strangulation of the bowel is perhaps the most important cause of this high mortality which can be reduced only by prompt surgery.

#### **REFERENCE**

Anderson, D. A. : *Ind. Jr. of Surg.*, 16 : 25 (1954).

### **Colonic Replacement of the Stomach**

Harrison reports on 30 cases treated with colonic replacement of the stomach and suggested that the technique is of value in the treatment of peptic ulceration and of early post-gastrectomy

syndrome. Colonic replacement ensures that the chyme enters the small bowel in the normal way through the duodenum and can thus be intimately mixed up with secretions entering the small upper bowel ; digestion and absorption can start at once and both are more complete.

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Harrison, B. B. : *Lancet*, 1 : 25 (1952).

**Intestinal Obstruction in the Newborn**

Macnab points out that the slow formation and passage of meconium through the intestine *in utero* is essential for dilatation of the gut to prepare it for proper function. Recent observation has shown that passage of meconium dilates the bowel in a short time following removal of obstruction. The author lists 222 cases of intestinal obstruction between 1926-51 of which atresia and stenosis accounted for 79 cases, meconium ileus for 13, neonatal Hirschsprung's disease for 12 and volvulus, peritoneal bands and mesenteric malformation for 62 cases. Neonatal intussusception, exomphalos, inguinal, and diaphragmatic and internal hernias accounted for a total of 38 cases.

Duodenal and intestinal atresia are characterized by bile-stained vomits and failure of meconium to appear in the stools by the third day of life is diagnostic. Treatment consists in resection of the atretic small intestine as also resection of the dilated and paralysed 6 in. of gut proximally, with end to end anastomosis. Both the proximal and distal segments are cut obliquely to provide a lumen of 2 cm diameter. The anastomosis is followed by a gastrectomy and passage of a soft rubber catheter into the jejunum. This maintains "a head of pressure" for the abnormal bowel to act on and dilate distal to the anastomosis.

In duodenal atresia a duodeno-jejunostomy is performed followed again by a gastrostomy and passage of soft rubber catheter into the efferent loop of jejunum through the duodeno-jejunostomy. Here the dilated segment is rested and the child is fed distal to the anastomosis.

*Meconium Ileus* : The association with cystic disease of the pancreas should be remembered. Enterostomy and irrigation with pancreatin solution has been helpful as also pancreatic extract by mouth.

*Hirschsprung's Disease* : Here rectal examination often reveals an undilated rectum which grips the finger. Often, passage of a finger relieves the obstruction failing which transverse colostomy can be life-saving.

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Macnab, G. H. : *Proc. Royal Society of Med.*, 48 : 303 (1956).

**STRESS**

T. H. Rindani

As defined by Selye<sup>1</sup> stress is the 'sum of all nonspecific changes caused by function or damage'. Although the idea of nonspecific reactions in production of disease was vaguely realised long before modern medicine began, the foundation for the approach to the causation of disease due to faulty adaptive responses of the body to noxious forces was laid by the eminent physiologist, Claude Bernard. He formulated the concept of the constancy of internal environment of the body as the basis of 'free and independent life'. It was suggested by him that damage by noxious forces called for adaptive reactions to maintain this constancy of the internal environment but the intensity of these reactions, at times, became more destructive than the damage caused by the disturbing factor itself and manifested as disease.

This concept was later extended and re-emphasized by Cannon in his famous doctrine of 'homeostasis'. According to Cannon a fixity of the internal fluid matrix of the body in the face of disturbances was maintained by a co-ordinated action of the sympatho-adrenal (medullary) system. This regulatory mechanism, however, was visualized to have limits and when overwhelmed broke down with consequent ill effects. The disturbing circumstances that called for homeostatic regulatory reactions were themselves designated as 'stresses'. However, in Cannon's thesis one sees the concept of homeostasis and the adaptive reactions as only concerned positively with protection of health and life and mediated through the autonomic nervous system and its effector humour only, the germs of the philosophy of stress as concerned in production of diseases being at best hidden. Moreover, the concept neither differentiated between specific and nonspecific responses nor attempted at any precise definition of stress.

## Stress

It was Selye who in a series of animal experiments carried out since 1936, observed that the organism responded in a 'stereotypical manner to a variety of widely different factors', and concluded that the 'stereotypical response which is superimposed upon all specific effects represents the somatic manifestations of nonspecific "stress" itself'. Selye has further elaborated this concept of stress locally in tissues by activity or by damaging agents. The stereotypical changes occurring in the body due to a systemic response are designated as "General Adaptation Syndrome", while those occurring locally in a tissue as the "Local Adaptation Syndrome". These syndromes occur in three stages along a time axis : the first being called *Alarm Reaction* consisting of initial 'shock' followed by a 'counter shock', the second during which the reactions of counter shock help to build up resistance with acquisition of adaptation and finally the *stage of exhaustion* when the resistance falls and the acquired adaptation is lost. It may be stated here that these syndromes give us totally inclusive concepts of damage and reaction to functional activity as well as to injury. It was shown by him that in the production of the general and local adaptation syndromes<sup>1</sup> the hypophysis-adrenocortical axis played an important (though not an exclusive) part. The hormones of these glands were shown to be concerned with regulation of the body's defences against stressful agents (stressors) and derailment of these hormonally controlled adaptive mechanisms caused diseases like nephrosclerosis, hypertension, arthritis, etc. Such diseases were, therefore, called as the "Diseases of Adaptation". As stated by Selye himself, 'the fundamental reaction pattern to topical stressors is a local adaptation syndrome with inflammation and to systemic stressors, the general adaptation syndrome. Various modifications of these two basic responses constitute the essence of most diseases'. One sees here the return of the constitutional pathology of Hippocratic and of Indian Ayurvedic Medicine after the intervening period of 'specific aetiology of the nineteenth century' following Pasteur's 'germ theory' of disease. In the battle between the seed and the soil as determining the causation of disease, the soil has again come to occupy a place of importance.

Selye's hypothesis, although, still in a controversial state amongst medical scientists has, without doubt, stimulated tremendous amount of fruitful thinking and research in the field of stress and particularly with regard to the role of endocrines in it. Research in stress as related to the causation of disease has also been advancing in the field of what may be called as the psychosomatic medicine, particularly under Wolff<sup>2</sup>. This worker has gathered evidence in support of the thesis that 'man confronted by threats, especially as they involve values and goals initiates responses inappropriate in kind as well as in magnitude. Such reactions integrated for one protective purpose and thus inappropriately used for another, can damage or destroy him'.

Interesting work has been presented recently by Basowitz and others<sup>3</sup> on the relationship between the anxiety of paratroop training of normal healthy young men and stress using several different indices of both. The authors observed that trainees who could not complete the course successfully showed greater psychological and somatic disturbance as seen by these tests, showing that these were more stress-sensitive subjects and the refusal to do the parachute jumping was only the final symptom. The authors further report that the biochemical indices of stress distinguished passing and failing subjects more clearly than the psychological measurements.

The mechanism of adaptive reaction in stress as visualized by Selye may be summarised by stating that whenever the body is facing a disturbance in its environment including even a physiological stimulus an impulse is mediated to the adeno-hypophysis either directly or via the hypothalamus. The pituitary gland in turn releases the hormones, ACTH and the somatotrophic (STH) hormones which acting directly as well as through the adrenal cortex bring about changes in several target structures in the body. The hormones of the adeno-hypophysis and adrenal cortex that take part in the defensive-adaptive reaction are classified as pro- and antiphlogistic hormones. The mineralocorticoids of the adrenal cortex and STH are pro-phlogistic while the glucocorticoids and the ACTH are antiphlogistic in action. These hormones act, amongst other targets, on the connective tissues, the kidneys and the lymphoid tissue of the body. The overall effect may be summarised as an increased connective tissue response in inflammation by pro-phlogistic and its inhibition by antiphlogistic hormones and an increased general resistance and a lowering of the local resistance by antiphlogistic hormones. The connective tissue reaction although mutually antagonised by the two sets of hormones in the body has synergistic action so far as the kidneys are concerned. Thus antiphlogistic hormones while counteracting the inflammatory reactions stimulated by pro-phlogistic hormones in the extrarenal tissues actually enhance them in the case of the kidneys.

Several objections to this concept of stress and diseases of adaptation have been raised but many of them have found answers in the rapidly developing knowledge in the field of endocrinology. Amongst these objections may be cited the argument that no endogenous mineralocorticoid was being secreted by the adrenal cortex which according to the 'unitarian' theory secreted only one type of hormone. The question, therefore, of balance between gluco- and mineralocorticoids, did not arise. The answer to this objection has been found not only in the demonstration of a very powerful mineralocorticoid, aldosterone, in the adrenal venous blood but also in its ability to antagonise the antiplogistic activity of glucocorticoids on extrarenal tissues and produce typical renal lesions attributed to the mineralocorticoids.

The mechanism of the regulation of the adrenocortical secretion itself has been invoked by Sayers as an argument against the concept of diseases of adaptation. According to Sayers<sup>4</sup> the blood level of adrenocortical hormones regulated the discharge of ACTH from the hypophysis by a 'feed back' mechanism. Accordingly, therefore, unless the blood level of the corticoid was low there would be no signal from pituitary for augmenting the secretion of the cortical hormones and a rise in corticoid level would inhibit ACTH secretion. Thus, a situation of excessive secretion from adrenal cortex in stress would never arise. Sayers<sup>5</sup> himself, however, has reported that plasma level of ACTH rises in stress even in bilaterally adrenalectomised animals. It is suggested by Selye<sup>6</sup> that this feed back mechanism which operates at near physiologic level, precisely fails in stress resulting in an excessive secretion of adrenocortical hormones. Similarly, the question of the mode of action of the adrenocortical hormones in influencing the metabolic and the morphologic changes of stress has been engaging the attention of the workers in the field. Thus, Ingle<sup>7</sup> has observed that for the changes in the body brought about by stress the presence rather than the increase in the quantity of the corticoids is necessary. He has designated this as 'the permissive' action of the hormones. At first sight this concept seems to contradict the possibility of causation of diseases of adaptation by an excess of the gluco- or mineralocorticoids, but as suggested by Ingle<sup>7</sup> himself, increased amounts of the hormones would be required even to support this permissive action during variable degrees of stress. There seems to be, a dose response relationship for the 'permissive action' of the hormones. Selye<sup>8</sup> looks at this problem from a different aspect by considering the 'permissive action' as but one of the phenomena of 'conditioning'. According to the concept of 'conditioning' of hormone actions, both the production and the action of the hormones in stress are influenced by several factors like age, previous exposure to stress, heredity, diet, etc. Thus the deleterious action of mineralocorticoid on the kidneys is enhanced by high sodium diet and therefore, lesions like nephrosclerosis, hypertension, etc. can be produced experimentally by mineralocorticoid more easily if combined with a high sodium intake. Similarly, the response of adrenal cortex to stress is modified by the nutritional status of the animal. In fact, it is the conditioning factors, like heredity, blood supply, nutrition, etc., that determine whether the stress will be a physiological adaptation or proceed to the causation of disease. This explains why individuals or different parts of an individual subjected to stress react differently.

One of the gaps in our knowledge of the mechanism of stress responses of the hypophysis-adrenal cortex is regarding the pathway(s) along which the impulse is carried to the pituitary gland. Several humoral mediators like adrenaline, histamine, etc. have been suggested, for, it has been established that neural pathways are not necessarily concerned in the activation of the adenohypophysis by all the types of stress. At best, the work in this direction has so far resulted in eliminating a number of agents as being indispensable for the release of the adaptive hormones under stress. On certain experimental grounds, the antidiuretic hormone of neurohypophysis has been claimed as the agent that stimulates ACTH secretion under stress (Mirsky and others)<sup>9</sup>, but in the elegant studies of Guillemin and Hearn<sup>10</sup> on tissue cultures of pituitary cells it was seen that while commercial vasopressin preparations increased the release of ACTH from these cells no such effect was observed with highly purified preparation of the hormone.

Attempts have been made to study the effects of pharmacological agents that may modify the response to stress or supply substances whose need may increase during the condition. Of interest amongst these are the so called 'antistress' agents. Thus it has been shown that in rats (Rindani)<sup>11</sup> adrenocortical activation by stress is prevented by pre-treatment with reserpine-free extract of *Rauwolfia serpentina* although the drug does not modify the action of either ACTH or cortisone (Rindani)<sup>12</sup>. In this connection it may be pointed out that this

## Stress

drug has been found to be of use in human hypertension and in certain psychiatric conditions (diseases of adaptation).

Just as systemic stress causes a train of metabolic and morphological changes in the body which has been designated as the general adaptation syndrome, fundamentally similar changes occur in local stress in the vicinity of the affected tissue. The sum of these nonspecific changes is called the local adaptation syndrome by Selye. It has been observed that introduction of local irritant in the tissues causes damage followed by inflammatory reaction, the course of which is influenced by the so called adaptive anti- and prophlogistic hormones. Peripheral antagonism between glucocorticoids and mineralocorticoids on inflammatory reactions has been demonstrated for hydrocortisone and compound S (Rindani)<sup>13</sup> and between the former and the natural powerful mineralocorticoid, aldosterone (Selye)<sup>14</sup>. The local adaptation syndrome, it may be pointed out again, is an inclusive concept, consisting of damage and defence. It has actually been observed that the anti-inflammatory action of the antiphlogistic hormone is related to damage or necrosis of the tissue for it is seen that the hormone by lowering the inflammatory potential of the tissue renders it more liable to necrosis by the irritant. It is for this reason that the action of cortisone cannot be likened to an 'asbestos suit' that protects the tissue from the 'fire' of infection because it may actually enhance local damage by reducing local resistance and also allow a systemic dissemination of the pathogen, by preventing the formation of a connective tissue barrier. The therapeutic use of glucocorticoids has therefore to be very judicious, namely, in conditions calling for an increase in general resistance of the body, in minimising unwanted inflammatory reaction like allergic inflammations around pathogens which if allowed to enter circulation would do no harm and in infections where the host reaction is far too excessive for the pathogen which may itself be mild and hence the disease process is essentially due to this excessive reaction.

The adaptive process in the tissue locally has been studied from a different angle. It has been observed that tissues subjected to stress by one type of irritant become more resistant to a cognate type of agent while their resistance to a dissimilar type of irritant is much lowered. Thus it is found that subcutaneous tissue previously treated with a particulate type of material like India ink which mobilises phagocytes increases the resistance to agents like kaolin—a cognate (particulate) substance—while exposure of the ink-pretreated tissue to croton oil (a dissimilar agent) caused marked necrosis showing that its resistance had fallen (Rindani)<sup>15</sup>.

As submitted before, although the concept of the adaptation syndrome is still a matter of controversy it has nevertheless directed research along very fruitful lines and brought about a new approach in medicine. To the list of the diseases of adaptation is now added the very interesting condition of profound electrolyte disturbance associated with renal arteriosclerosis and a reversible hypertension directly related to adrenocortical hormonal imbalance, namely, "Primary Aldosteronism" described by Conn<sup>16</sup>. This puts Selye's concept of diseases of adaptation on a very formidable basis and it would be well to end this article with the remark of Conn himself, 'if the effects in man of chronic excessive and imbalanced mineralocorticoid activity are sought (and this is postulated as the predominant factor in the evolution of diseases of adaptation) primary aldosteronism is a good place to look'.

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**SUBMUCOUS FIBROSIS OF THE MOUTH AND PHARYNX—See MOUTH AND PHARYNX, SUBMUCOUS FIBROSIS OF THE**

**SULPHONAMIDE DRUGS, THE PRESENT STATUS OF**

V. S. Prayag

Twenty-one years have passed since the sulphonamides were introduced in the practice of medicine. A large number of these compounds have been introduced in the last two decades but few are in use now as those discarded with time had many disadvantages in their use. With the new era of antibiotics the sulphonamides went into background as they have been overshadowed by the former but some of them are still useful in practice.

**Antibacterial Action.**—The sulphonamides are active against numerous Gram+ve and Gram—ve bacteria; the haemolytic streptococci and pneumococci are the most sensitive in the former group. Staphylococci are moderately sensitive especially to sulphadiazine, sulphadimidine, sulphathiazole and sulphamerazine. *Streptococcus viridans* is slightly sensitive and enterococci completely insensitive. Among the Gram—ve bacilli, the shigellae and *B. coli* are highly sensitive to sulphonamides. Meningococci are for the most part highly sensitive though a few strains are partially resistant. *H. influenzae*, *H. pertussis*, claustridia, pasteurellae, brucellae, and actinomyces are moderately susceptible.

Sulphonamides have no effect against *P. vulgaris*, *Pseudomonas pyocyanea*, the viruses and protozoa.

**Synergism and Antagonism:** Synergism between two sulphonamide compounds has now been proved and multiple sulpha combinations are used to enhance the antibacterial action of the individual members and to minimise certain toxic effects. Para-aminobenzoic acid in minute doses antagonises the action of sulphonamides. Procaine and benzocaine which contain this should be avoided when sulphonamides are being used. Barbiturates should also be used with caution. Administration of aldehydes, e.g. hexamine or urotropine, together with the sulphonamides results in formation of compounds which are precipitated in the urine and cause painful micturition and hematuria (Staub, 1943).

**The Choice of Sulphonamides.**—(1) *Sulphamethazine* or sulphamezathine is highly soluble, has high absorption rate and its excretion by the kidney is much more rapid than sulphadiazine. It is one of the least toxic of the sulphonamides as also one of the most suitable for routine use. Hawking and Lawrence<sup>1</sup> particularly recommended it in pneumococcal infection, however severe. It is not as suitable as sulphadiazine for therapy of meningitis.

(2) *Elkosin* appears to be slightly superior to sulphamezathine for systemic treatment in pneumonia, cerebrospinal fever and urinary infections. It rarely causes any kidney damage, and excretion by kidneys though slow, is more rapid than is the case with sulphamerazine.

(3) *Irgafen* has a more selective action than the other sulphonamides. There is believed to be a double action on the pneumococcus; it is bacteriostatic and also acts on the resting phase interfering with respiration. It has a slow excretion and is also useful in the prevention of infections. Toxic effects are mild<sup>2</sup>. Of these anaemia is the most frequent though mild.

(4) *Formo-Sulphathiazole*: It resembles succinyl and phthalylsulphathiazole in being but little absorbed from the intestine. It however differs in certain other respects. It is active against *Streptococcus foecalis* and against the typhoid bacillus and cholera vibrio *in vitro*.

(5) *Succinyl Sulphathiazole* (Sulphasuxidine): It has by itself little bacteriostatic effect. It acts by liberating sulphathiazole which acts locally in the bowel. It is very insoluble in water and is not absorbed to any appreciable extent as such. It is practically nontoxic and has been used successfully in the treatment of bacillary dysentery.

*Sulphadiazine* is slowly but completely absorbed from the intestine. About 20 per cent of the drug is bound to protein and there is ready diffusion into exudates and body fluids. It is only sparingly soluble in urine and may cause anuria or hematuria. It has been extensively used for prophylaxis and for topical application.

*Sulphacetamide* readily penetrates the cornea and conjunctiva when applied to the eye as a 30 per cent solution of the sodium salt. It penetrates the skin more effectively than other sulphonamides. Toxic effects are uncommon.

**Sulphonamides and Antibiotics:** Reevaluation of sulphonamide therapy is presented by Ellard M. Yow<sup>2</sup>. The sulphonamides are, according to him, the preferred antimicrobial agents for



meningococcic infections. No clinically resistant strains of meningococci have been encountered. Sulphonamides are as effective as tetracycline in bacillary dysentery and chancroid and probably as effective as any other antibacterial agent in anthrax, cholera, plague, inclusion conjunctivitis and trachoma. Because of their diffusibility and additive antibacterial effect, sulphonamides are often of definite value when combined with antibiotics. They are as effective as any other single agent in infections due to anaerobic and aerobic actinomyces and probably more effective when combined with penicillin or iodides. Beeson gives both penicillin and sulphonamides until cultures become negative. Sulphonamide therapy is then continued for a month after all sinuses have stopped draining.

Sulphonamides are being combined at present with various antibiotics like penicillin, chloramphenicol (Sulphamycetine), etc. These combinations have different advantages, the chief being that both drugs provide effective therapy at less cost.

**Non-chemotherapeutic Sulpha Derivatives.**—With the introduction of a large number of antibiotics the progress of sulpha compounds was slowed down to some extent but new fields were opened up with the introduction of two new compounds, viz.

- (1) Acetazolamide or Diamox.
- (2) Oral antidiabetics, e.g. Invenol, Rastinon, etc.

*Acetazolamide* is an oral diuretic which acts by inhibiting carbonic anhydrase and is found useful in congestive heart failure, hyperpotassaemia and glaucoma (Ishwariah).<sup>3</sup> It is not so useful in renal oedema, emphysema and liver cirrhosis. By producing acidosis it can be of use in epilepsy especially in children. Toxic effects are rare and may be manifested by giddiness, numbness of the limbs, paraesthesia and general weakness, sleepiness, etc. Acetazolamide can be combined with mercurial diuretics when its action is further enhanced and though of less harm to kidneys, its action seems to be much less than the mercurials.

*Invenol* or BZ55 is a yellow crystalline substance, and is a derivative of urea, viz. n-butyl sulphanilyl urea. In dogs and rabbits it causes a fall in blood sugar level. In human beings also it causes a fall in blood sugar and as an oral antidiabetic it possesses the following advantages :

- (1) It has a wide margin of safety.
- (2) In those who need insulin, the dosage of insulin could be reduced by combining with Invenol.
- (3) Serious hypoglycaemic states are not induced by it even in high doses.

The mode of action is only speculative. It is thought to exert an inhibiting effect on the alpha cells of the islets of the pancreas. The drug is of no use in diabetic coma, in juvenile diabetes and diabetics of long duration, over 10 years.

Because of the possibility of its toxic effects, being a sulpha compound, a substitute was found out and this is termed as D 860 or Rastinon. This is safer to use over long periods, and the experience of various workers seems to be encouraging in its use in certain types of diabetic cases.

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#### SYPHILIS, SERODIAGNOSIS OF

B. A. Daruvala

Until the turn of the century the diagnosis of syphilis was an art, and depended entirely on the skill of the physician to interpret the clinical manifestations observed in the patient. In Berlin, on the 10th May 1906, Wassermann, Neisser and Bruck published the results of their experiments on the serologic diagnosis of syphilis. What subsequently came to be known as the Wassermann test was believed by its authors to be a specific test for the diagnosis of syphilis, they having employed saline extracts of syphilitic liver as an antigen. Within a year, Marie and Levaditi falsified this claim to specificity, employing saline extracts of normal tissues as antigen for the test, and these observations were soon confirmed by Weil and Landsteiner et al. The saline extracts were later replaced by alcoholic lipid extracts, and antigens prepared from these proved

more specific and more sensitive than the original antigens prepared from aqueous extracts of infected tissues.

Michelis, in 1907, published the results of his precipitation studies on syphilitic sera. Since then many more flocculation, precipitation and clarification tests have been devised, such as Kahn, Kline, Eagle, Price, Hinton, Mazzini, Rein-Bostak, Meinicke, V.D.R.L. and others.

In both the complement fixation and flocculation tests the antigen employed is a lipid extract of dried beef heart. The fact that positive tests are usually specific for syphilis suggests that these lipid extracts of animal tissues, so far as laboratory procedures are concerned, have much the same antigenic properties as treponemes.

Wassermann test, a complement fixation test, is based on the principle of Bordet and Gengou that complement is fixed by an antigen and its antibody. A haemolytic system is employed as an indicator. Antibodies capable of haemolysing (sheep's) red blood cells in the presence of complement fail to do so when the latter is missing. If the sample of serum being tested contains reagin (syphilitic antibodies) the antigen-antibody complex fixes the complement, leaving none for the haemolytic system, and haemolysis fails to take place, the test is positive. Hecht and Kolmer are two other complement fixation tests in common use.

In flocculation tests, the reagin combines with the antigen to form visible aggregates as a result of stable hydrophile colloids being replaced by the unstable hydrophobic colloids. Chemical, serological and clinical evidence all support the view that the complement-deviating and flocculating antibodies belong to two distinct types.

Serology of syphilis has made spectacular advances in recent years and the achievements here have more than kept pace with advances in other fields of medicine. More sensitive and more specific serologic procedures are now available since the introduction of better-defined lipoidal antigens. Pangborn, in 1941, isolated a serologically active phospholipid, "cardiolipin", from the crude alcoholic extract of beef heart. When used alone it is anti-complementary. Purified lecithin alone has no antigenic activity. A mixture of cardiolipin and lecithin is not anticomplementary and acts as an antigen. The addition of cholesterol to a non-optimal mixture of the two increases its antigenic effect. Cardiolipin carries most of the serologic activity of beef-heart extract and improves the specificity and sensitivity by eliminating many impurities which characterize the crude antigens. The cruder lipoidal antigens have now been replaced by the more sensitive cardiolipin lecithin-cholesterol antigen mixtures. The proportions and absolute concentrations of these components vary in the antigens employed for different tests; an antigen suitable for one technique may not be satisfactory for another. A stained cardiolipin antigen has been recommended as an improvement on the ordinary antigen for use with flocculation and precipitation procedures. The addition of Sudan III gives satisfactory results. By staining the flocculi a yellow ochre colour, it improves the readability of the test without in any way interfering with its sensitivity or its keeping properties.

Phosphatides similar to cardiolipin, and suitable for use in serologic tests for syphilis have been isolated from vegetable sources, such as wheat germ (sitolipin), soya bean, maize, carrot, etc. Lecithin obtained from egg yolk can satisfactorily replace beef heart lecithin. As cardiolipin and lecithin have now been chemically defined and suitable synthetic products may soon be available, and as cholesterol can be obtained in a chemically pure form, it should be possible, after determining their optimal proportions, to develop a mixture of standard sensitivity and specificity that can be even dispensed by weight.

The most recent additions to our diagnostic armamentarium are the tests employing *Treponema pallidum* as antigen. The *Treponema pallidum* immobilization (TPI) test was described by Nelson and Mayer in 1949, and is the only test for syphilis in which the living infective agent is used as an antigen. Other tests such as *Treponema pallidum* agglutination (TPA) test, *Treponema pallidum* immune-adherence (TPIA) test, and *Treponema pallidum* complement fixation (TPCF) test employ killed pathogenic treponemes or extracts of them. The TPI test is an excellent verification procedure but is not fit to be used as a test of cure.

The tests employing treponemal antigens detect an antibody that is different from the reagent that causes a positive reaction in the older types of tests. (It is doubtful if the reagins found with the routine serologic tests are true antibodies). The abbreviation STS for standard (serologic) tests for syphilis, is generally used to denote the older tests employing lipoidal antigens.

## Syphilis, Serodiagnosis of

The newer serodiagnostic tests, like TPI, TPA, etc., employing treponemal antigens, in spite of the obvious advantages, cannot replace the routine STS of the reagin type which are in common use. Though it is recognised that the antigens employed in these latter tests are not specific in the true biologic sense, these tests have attained a high degree of sensitivity and specificity and offer valuable information. Cardiolipin antigens are definitely more sensitive than the crude lipoidal antigens, but recent work throws doubt on their claim to greater specificity. It must be conceded, however, that they have been found definitely more specific in cases of malaria. All treponematoses—syphilis, yaws, pinta, and bejel, give “specific” positive reactions to serologic tests.

One must be properly acquainted with the different serologic procedures and their relative sensitivities to be able to correctly assess the result of any test or group of tests. Though not much difference is observed in the rising phase of the sensitivity of these tests, in the static or declining phase the difference may be marked. In a battery of tests, at any particular time, some may be positive and others negative, and a proper interpretation of such results would be difficult unless one is aware of their individual characteristics.

Time and temperature have considerable effect on the keeping qualities of whole blood and serum, and every effort must be made to avoid contamination of samples and prevent haemolysis. What part these play in the possible production of inhibitory and toxic factors, or in the production of non-treponemal reagin has not been determined.

Quantitative tests, carefully performed and intelligently interpreted, may provide useful information. They help to evaluate the response to treatment, to differentiate congenital syphilis from passive reaginemia, to distinguish a biologic false positive from a true positive reaction, and sometimes to detect a reinfection.

There are obvious disadvantages in the “unit” system of recording quantitative results. Identical findings with two or more tests are thus expressed in numerical values which may be entirely different. A useful suggestion is to express them in dilution reactivity end-points, i.e., the greatest dilution at which the tested specimen gives a positive result. The term “dils” is employed instead of units to express the results. Serologic reactions of identical intensity, even with different tests, will then give the same results in dils.

Primary syphilis may or may not be associated with positive STS. A positive reaction is obtained ten days or more after the appearance of the chancre, and may take as long as three months, rarely longer. A positive dark field result from a competent technician, will establish the diagnosis beyond doubt. The effect of antibiotic drugs, administered at the appropriate times even though for some other disease, has to be taken into account, as such therapy may alter the clinical and serological course of the disease.

In the secondary stage the STS are always positive. The exceptions are so few, that it is difficult to entertain the diagnosis of secondary syphilis in the absence of serologic confirmation.

The diagnosis of latent syphilis rests on persistently positive serologic findings in the blood, there being no other corroborative clinical or laboratory evidence of syphilis elsewhere (including a normal C.S.F. report). Past history of syphilis may or may not be forthcoming. These cases often present difficulties in arriving at a proper diagnosis. (It has now been realised that, in rare instances, the only evidence of syphilis in these cases may be a positive TPI or TPA test, and even the blood STS may be negative).

Late symptomatic syphilis, i.e., late benign, cardiovascular, or neurosyphilis may occasionally be associated with negative STS in the blood. Biopsy examination, X-ray examination and therapeutic tests may be useful. Positive treponemal antigen tests will help to establish the diagnosis.

Positive serologic reactions in pregnancy may sometimes be difficult to differentiate from biologic false positive reactions. It is not fair to withhold antisyphilitic treatment, unless there is irrefutable evidence to show that the reactions are of the biologic false positive type.

A negative serologic reaction in the new-born does not always exclude the diagnosis of congenital syphilis. Positive reactions may develop later if the infection was acquired late in pregnancy. Similarly a positive serologic reaction soon after birth, in the absence of any clinical evidence of syphilis, may merely indicate a passive transfer of maternal antibodies to the foetus, described as “syphilotoxaemia” or “passive reaginemia”. The serologic reactions in such cases gradually return to negative. The sero-reversal is usually complete within two months, though rarely

it may take as long as five months. If on the other hand, the child's serum shows a steady upward trend, the diagnosis of syphilis will be confirmed. The not infrequent association of positive complement fixation tests with negative flocculation tests in cases of passive reaginæmia is explained on the concept of two different antibodies, the complement-fixing antibody which may pass through the placenta, and the flocculating antibody which may not. Late congenital syphilis may be associated with weak positive or negative STS.

In treated syphilis reversal to sero-negativity does not coincide with the time of cure. Though in early syphilis sero-reversal may be complete within two years, in late symptomatic or latent syphilis and in late congenital syphilis sero-reversal to negativity rarely takes place within 5 years and may take longer. In infections of more than ten years' duration the serological decline is very slow, if it occurs at all. The older the disease the longer it takes to attain sero-negativity. Besides the stage of the disease at the time when treatment is started, other factors such as the serologic titre at the onset of therapy, the sensitivity of the serologic tests employed and the immunologic response of the individual have also to be considered. The rate of fall of the serologic titre from a given level is significantly more rapid after treatment for a first infection than after treatment for a reinfection, probably because of a larger immunologic stimulus in the latter instance.

Cerebrospinal fluid examination should be done in all cases of syphilis and particularly late syphilis. The tests provide a reliable index of the activity of neurosyphilis, and also serve as a useful guide to the efficacy of treatment. The examinations include (1) cell count, (2) total proteins, (3) globulin estimation (qualitative), (4) serologic tests for syphilis, and (5) colloidal gold or mastic reaction. Positive serologic tests alone indicate the specific nature of the disease. After treatment, if the disease process has been arrested, there is a gradual decline to normal values. The cell count returns to three or less per ml within six months. The proteins may take longer, upto two years, whereas five years or more may lapse before complement fixation and colloidal reactions reach normal. There is no constant correlation between spinal fluid results and clinical findings or symptoms. Definite clinical improvement may be associated with spinal fluid findings indicative of an active syphilitic process. The reverse may also be the case, as in burnt out tabes dorsalis, where the spinal findings may be normal and clinical evidence of neurosyphilis persist, probably due to a permanent neuraxis damage.

Bacterial contamination of the spinal fluid will interfere with serologic tests and may affect the total protein determinations and the colloidal tests. The presence of blood, even in minute quantities, can alter all laboratory findings, serologic tests, protein estimations, colloidal tests and cell counts. A total cell count, performed as a routine with all C. S. F. specimens may help draw attention to the presence of blood. Centrifuging out the blood cells will not remove the serum components from the spinal fluid.

The term "biologic false positive reaction" is used to describe the positive results obtained with sera from non-syphilitic patients with the routine serologic tests for syphilis, employing either the crude lipoidal or the cardiolipin antigens. False positive reactions may be due to causes (1) in the patient himself, (2) in transit (of the specimen to the laboratory) or (3) in the laboratory. The causes in the patient include all those diseases and conditions which are known to cause false positive reactions and these are grouped under the term "biologic false positives". Those under (2) and (3) belong to the category of "technical false positives" and may result from such diverse causes as bacterial contamination or haemolysis of the blood sample, the use of faulty containers, an improper antigen, a wrong technique, etc. Little is known about the actual mechanism causing biologic false positive reactions, or for that matter, about the true syphilitic reactions.

The frequency of false positive reactions varies according to the different population groups and according to the tests employed. In a malarial district for example, the percentage of false positive reactors will be higher. With a continued decrease in the incidence of syphilis, a relative increase in the percentage of biologic false positives is to be expected. For any particular disease the frequency of biologic false positive reactions will vary with the type of serologic tests employed, the number and frequency of the tests performed during the course of the disease, the stage of the disease, and the individual immunologic response; sera of certain individuals seem to be more easily precipitated into serologic reactivity by certain non-syphilitic diseases.

Biologic false positive reactions may be acute or chronic. The acute reactions are seen in association with a variety of infections, bacterial, viral, plasmodial, rickettsial or protozoal.

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These return to normal within a short period of time not exceeding six months. Acute biologic false positive reactions have been observed in infants after immunisation against pertussis, diphtheria, tetanus, and small pox, and also during or after an attack of measles, chicken pox, small pox or an upper respiratory tract infection.

Chronic biologic false positive reactions, are positive reactions to serologic tests for syphilis observed in non-syphilitic (and non-treponematic) individuals, which persist for a long period, for many years or even a life time, and are not associated with the disease conditions responsible for the acute type of reactions. Of recent years it has been observed that chronic biologic false positive reactions are often associated with certain collagen diseases like rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa or more rarely with Hodgkin's disease or Gaucher's disease. These serologic phenomena are often the earliest indication and may precede the onset of clinical manifestations of the disease by many years. Leprosy is a disease which is often associated with chronic biologic false positive reactions.

Various laboratory procedures have been devised to differentiate syphilis from other non-syphilitic conditions associated with positive STS, such as the Wassermann confirmation test, Kahn verification tests, Hecht verification test, Witebsky confirmation test, Rein-Pillemer inhibition test, the Neurath (cuglobulin inhibition) test and a few others, but none of them has given very satisfactory results. Special antigen formulae, varying the proportion of the different components in the cardiolipin antigen or altering their absolute concentrations, have also been tried out without much success. The only definite and reliable method to distinguish a "true positive" from a biologic false positive, is by employing one of the newer serologic tests with a treponemal antigen TPI, TPA, etc.

The *Treponema pallidum* immobilization test was first described by Nelson and Mayer in 1949, and is the only test for syphilis where living organisms are employed as antigen. The immobilizing antibodies detected by this test are not identical with the reagins demonstrable with the lipoidal antigens. This test too, like the older STS, cannot distinguish between the different treponematoses,—syphilis, yaws, pinta and bejel.

In the TPI test live pathogenic treponemes (Nichols' strain) are employed as antigen. A mixture of antigen and antibody (patient's serum), together with active guinea-pig serum as complement, is incubated under anaerobic conditions at 35°C. for 18-24 hours, and then examined by dark field microscopy. Immobilization of the treponemes is observed if the serum contains antibodies. A series of controls is employed for the test, one of them containing inactive complement. The test is positive if motility determinations show a difference of more than 50 per cent between the tubes containing active and inactive complement, doubtful if the difference is between 20 per cent and 50 per cent, and negative if the difference is less than 20 per cent. When the control tube with inactive complement shows more than 30 per cent immobilization at the end of the incubation period, the test is inconclusive. The results may be expressed quantitatively, by determining the highest serum dilution that produces immobilization of 50 per cent of the treponemes.

This test possesses a very high degree of sensitivity, near 100 per cent for cases of late syphilis, acquired and congenital. In primary and secondary syphilis it may be negative as it takes longer than the routine STS to become positive. About 60 per cent of primary and 90 per cent of secondary cases give positive reactions with the TPI test.

It is also a highly specific test, and one of its chief uses lies in distinguishing biologic false positive reactions obtained with the routine STS.

Except in cases of primary and secondary syphilis, where the difference is not so marked, the TPI test takes much longer than the routine STS to become negative after treatment. In late acquired or congenital syphilis, with few exceptions, the immobilizing antibody unlike reagin, persists in the serum indefinitely irrespective of the anti-syphilitic treatment given. Like the Mantoux reaction in tuberculosis, a positive reaction can only signify that the patient had a syphilitic infection at some time, and in a treated case it cannot be taken to indicate the need for further treatment.

The test may profitably be employed (1) to detect biologic false positive reactions, (2) to diagnose late latent syphilis with a negative serology (with STS), (3) to determine the nature of obscure lesions attributable to late acquired or congenital syphilis, (4) to determine the syphilitic aetiology in certain treated and untreated cardiovascular and nervous diseases,

(5) to establish the diagnosis of a treated case of late syphilis in retrospect, (6) to interpret intermediate (doubtful) results obtained with the routine STS, and (7) occasionally to differentiate between a relapse and reinfection.

There are many technical difficulties in its performance. So far it has been impossible to grow pathogenic *Treponema pallidum* on an artificial medium. The Nichols strain has been maintained by passage on live rabbits and new antigen suspensions have to be prepared from fresh rabbits each time. Besides being a tedious and expensive procedure, such "biological" antigen suspensions are likely to be more variable than antigen suspensions prepared from a proper stock antigen. Great care is needed to maintain completely sterile conditions throughout the performance of the test. Another major difficulty one has to contend with is the avoidance of *in vivo* sensitization of the treponemes. This has been achieved by the use of nitrogen mustard, X-rays or cortisone, the last one being usually preferred.

The TPI test is mainly a diagnostic test, and is not yet fit to be used as a test of cure. Complement fixation and flocculation tests must continue to be the methods of choice as laboratory aids for the detection and management of syphilitic infection. Although the TPI test is highly specific there is evidence that non-treponemal reactions do occasionally occur.

Immobilizing antibodies, just like reagins are passively transferred through the placenta and take a longer time to disappear than reagin. Quantitative STS will be more useful in such cases than the TPI test to determine the presence of syphilis in the newborn.

The *Treponema pallidum* agglutination test (TPA), the *Treponema pallidum* immune adherence test (TPIA) and the *Treponema pallidum* complement fixation test (TPCF) have certain definite advantages over the TPI test. In these cases killed treponemes are used as antigens; these antigens can be stored for months in a refrigerator and can be supplied to laboratories which do not have the facilities to perform the more complicated TPI test.

In the TPA test, *in vivo* sensitization of *Treponema pallidum* may occur during the development of orchitis as in the case of the TPI test, leading to spontaneous agglutination. Pre-treatment X-irradiation of the rabbits with 600 r, or the employment of cortisone, about 6.0 mg per kg of body weight of the animal given intramuscularly, starting from the third day after inoculation and continued upto the time the animal is sacrificed, may obviate these difficulties. Besides preventing *in vivo* sensitization of the organism, cortisone also helps in obtaining maximum yields of antigenic material. The optimum time of harvesting, which is dependent on the rate of development of the orchitis is an important factor in avoiding *in vivo* sensitization of the organism, and should not be unduly prolonged. The rate of development of orchitis is dependent on various factors, the strain of the organism employed, the size of the inoculum, environmental temperature, the type of pre-treatment employed, etc.

With the TPA test, readings are made after dark field examination of the samples from the agglutination tubes, and this presents certain difficulties. To properly evaluate the results one has to determine the degree of clumping and the number of organisms observed in the field, and though there may not be much difficulty in identifying a strongly positive or a frankly negative result, the intermediate phases are often difficult to interpret. Quantitative results are also difficult to express, for the same reasons.

The *Treponema pallidum* adherence-disappearance (TPIA) reaction is a test which is still in the developmental stage, but offers many obvious advantages over the TPI test. Suspensions of killed treponemes are generally used here, eliminating the risk inherent in the use of the live organism. It is cheaper than the TPI test and quicker and easier to perform. There are two stages in the test. First, the immune adherence of sensitized treponemes to normal red blood cells, and next the disappearance of these treponemes as a result of leucocytic phagocytosis. The first stage, or the immune adherence phenomenon alone can be used for the detection of the specific antibody.

The antibodies demonstrated in the TPIA test appear to be closely related to the immobilizing antibodies in the TPI test, whereas the antibodies detected in the TPA test bear a closer resemblance to reagins demonstrated in the usual serologic tests.

The *Treponema pallidum* complement fixation (TPCF) test is another test employing treponemal antigen. The test has been carried out with virulent treponemes or extracts thereof. Price et al, recently published results of one such test which they called the Treponemal Wassermann Reaction (TWR). The reactions obtained with this antigen were reproducible and the results

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obtained compared favourably with those of the TPI test, both as regards sensitivity and specificity. This test seems to have many technical advantages over the TPI test.

A *Treponema pallidum* complement fixation test has also been performed with Reiter treponeme as antigen (RCFT). It was found to be quite satisfactory for the diagnosis of acquired syphilis, though not as reliable for cases of congenital syphilis.

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**SYPHILIS OF THE CARDIOVASCULAR SYSTEM—See CARDIOVASCULAR SYSTEM, SYPHILIS OF**

## TEMPORAL LOBE, FUNCTIONAL DIVISIONS OF; PSYCHOMOTOR EPILEPSY

E. P. Bharucha

**Functional Divisions of Temporal Lobe:** The temporal lobe is anatomically divided on its supero-lateral aspect into superior, middle and inferior convolutions. Its inferior and medial aspects include the hippocampus (including Von Ammon's Horn) the amygdaloid complex and the uncus.

Physiologically (Williams, 1957)<sup>3</sup> the temporal lobe consists of

- (i) A special cortex subserving hearing, smell, taste and balance.
- (ii) Association areas concerned with the interpretation of sensation and production of emotional feeling.
- (iii) The "visceral" brain including the hippocampus, uncus and the neighbouring cortex in the inferior frontal, anterior temporal areas and also the insula.



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**The Special Sensory Cortex :** (a) The auditory cortex lies in the middle of the superior temporal convolution. Epileptic discharge in the auditory receptive area itself—area 41, gives rise to hallucinations of crude sounds whereas discharge into the neighbouring auditory association areas (42 and 22) produce elaborate auditory verbal and musical hallucinations. The intimate connections of the auditory with the visual association areas explains the combination of visual with auditory hallucinations in the dreamy state. Vertiginous epileptic sensations are associated with lesions of the area.

(b) The olfactory cortex has not been localised in man. Olfactory stimulation produces no electrical potentials in the hippocampus. Though lesions in this area produce hallucinations of smell (uncinate fits of Jackson) the hippocampus is no longer considered to be a station in the olfactory pathway.

(c) Taste—stimulation of the island of Reil produces a sensation of taste.

**Association Areas :** (a) *Emotional Responses :* The neocortex of the 2nd and 3rd convolutions of the temporal lobe inhibits subcortical mechanisms (rhinencephalon) concerned with the rage reactions. Epileptic discharge from lesions in this area produce rage, fear, depression or pleasure.

(b) *Other Sensations :* Visual delusions (micropsia, macropsia) temporal distortions such as the *déjà vu* phenomenon and capacity to recall a past scene suggest that visual memory is stored in this area.

**The Visceral Brain :** Stimulation of the orbito-frontal cingulate cortex and posterior temporal tip anterior insula, and hippocampus produce alterations of blood pressure, pulse, sweating, piloerection, gastric mobility, micturition and defaecation.

**Psychomotor Epilepsy.**—The term psychomotor epilepsy is now largely employed to include paroxysmal alterations of consciousness, emotion, (fear, rage, pleasure), mood (depression or elation) together with auditory and hallucinatory disturbances followed by semipurposive movements and behavioural disturbances often culminating in a generalised convulsion. The majority of these cases have an electrical spike focus in one or both temporal lobes in the E.E.G.

**Pathogenesis:** Penfield et al (1953) feel that head moulding during birth results in a tentorial herniation of the temporal lobe with occlusion of arteries resulting in sclerosis of the mesial and inferior portions of the lobe. Others consider, anoxia associated with convulsions, caused by infectious fevers (measles and chicken pox) and gastroenteritis to be more important factors.

**Clinical Picture :** This consists of an aura and the seizure proper. It is the aura preceding the automatism which suggests to the clinician a temporal lobe localisation of the attack.

**The auras of temporal lobe epilepsy :** The auras, to some extent, depend on the site of discharge. Williams (1957) has classified them into (i) antero-medial (uncinate) and orbito-frontal. In this group there are autonomic changes—pallor, fear, aggressive behaviour and a dreamy state, perceptual delusions and an olfactory sensation—Jackson's uncinate fits.

(ii) Sylvian : Abdominal sensation, epigastric aura, fear, aggression, a dreamy state and focal motor changes in the face and aphasia.

(iii) Anterior-temporal : Psychological disturbance with fear and emotional change. Autonomic changes, formed visual hallucinations, *déjà vu*.

(iv) Mid temporal : Formed and unformed auditory hallucinations or vertigo. Disorder of time perception. Sense of familiarity, depersonalisation or derealisation.

(v) Posterior temporal : Visuo-spatial disorders. Illusions about the shape of limbs, autoscapy, pleasurable and unpleasurable dreamy states.

**Seizure proper :** These may be of 3 types—1. Minor seizure, consisting of the aura alone. 2. Amnesic attacks without convulsions.

Following the aura described above, the patient becomes dazed, unaware of his surroundings, and indulges in semipurposive automatic movements which are in keeping with the sensation expressed in the aura i.e. rubbing the abdomen, in the epigastric aura. This lasts from a few seconds to a few minutes and is followed by a period of confusion when the patient may



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perform purposive but inappropriate movements, such as shutting a door, undressing, becoming boisterous and attacking people. This is known as post-epileptic automatism.

3. Major convulsive seizures : The aura may be followed by a generalized convulsion in some cases at one time and by automatism at another.

*Treatment—Medical* : Mesantoin, Mysoline (primidone) and Phenurone are the most valuable drugs. If a well defined E.E.G. focus exists in one temporal lobe, surgery is indicated.

*Results of Surgical Excision* : Penfield and Jasper (1954) emphasize the importance of removing the uncus, amygdaloid nucleus and hippocampal gyrus at the time of doing a partial temporal lobectomy. Reports from various centres suggest that approximately one half of the patients are benefited. The other half continue to have fits. In lobectomized patients it has been found that spike foci may occur elsewhere in same hemisphere or mirror foci in the opposite temporal lobe may become activated.

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**TESTS, POST-MORTEM LIVER FUNCTION**—*See* LIVER FUNCTION TESTS, POST-MORTEM

**TESTS OF PULMONARY FUNCTION**—*See* PULMONARY FUNCTION TESTS

**THROAT DISEASES**—*See* EAR, NOSE AND THROAT DISEASES

## THROMBOCYTOPENIC PURPURA, ACUTE IDIOPATHIC, TREATMENT OF

R. Subramaniam

In the past five or six years it has been realised that idiopathic thrombocytopenic purpura and auto-immune haemolytic anaemia have much in common. There are two chief varieties, the acute self-limited one and the chronic variety. Acute cases come on suddenly in a person who has not been found to have platelet deficiency previously, run a violent course and at the end of a few weeks or few months subside leaving no trace of the original condition. Since this disorder is seen particularly in children after an acute infection or in individuals who have become sensitized to drugs, it is concluded that an immunologic disturbance although it be a temporary one may be responsible in many of the acute cases. In chronic cases also there may be violent haemorrhagic episodes but they have a tendency to persist in a mild form from year to year. If an immunologic mechanism is present in chronic cases it must be of the nature of a continuously self-perpetuating one. In chronic cases splenectomy is a recognised procedure although the rationale for this procedure is questioned, relapses may occur even after operation, even so late as 5 to 10 years after. In the treatment of a case of idiopathic thrombocytopenic purpura, a detailed history is important to determine whether there has been any exposure to drugs or chemical agents or whether there is any underlying latent disease such as disseminated lupus erythematosus or any infection. One should particularly look for lymph node enlargement and hepato-splenomegaly as they may suggest the aetiological mechanism with an otherwise normal blood picture exhibiting thrombocytopenia. One may expect recovery to occur in weeks or months provided the patient is kept alive and free from serious bleeding till recovery occurs. In acute cases, cortisone, hydrocortisone, or prednisolone orally or ACTH parenterally is indicated, the dose being 300 mg of cortisone, 150 mg of hydrocortisone, or 45 mg of prednisolone. In the absence of anaemia no transfusion is indicated. The most important point is whether one should carry out splenectomy or not. This depends upon the severity of the bleeding. Prognosis is considered severe when the patient is kept under observation and given medical treatment. If on the other hand, there were severe bleeding, a previous history of epistaxis, extensive bleeding from the mucous membrane, haematuria, melaena or signs of intracranial haemorrhage, then immediate splenectomy is indicated. In these cases steroid therapy is required and is given intravenously by drip till the patient is in a position to take it orally. In the absence of anaemia without waiting for transfusion and steroid drip, patients have been submitted to splenectomy successfully in the

hands of skilled surgeons, and there has been practically no mortality. Experience of surgery has shown very little operative bleeding in spite of extensive spontaneous haemorrhage. Dramatic cessation of bleeding has been observed sometimes. The one difficulty that was expressed with regard to splenectomy was that there was no certain guide as to when splenectomy has to be performed and the decision to operate remained largely a matter of individual judgment of the case. Emergency splenectomy is best indicated in haemorrhages where it is pronounced, particularly in intracranial haemorrhage or where it was felt that the blood loss was very severe causing exsanguination. Elective splenectomy was advocated where platelet antibodies have been demonstrated or where steroid therapy was not effective.

Bone marrow biopsy may give a clue to the prognosis. If there was abundance of eosinophilia it was considered to be of good prognosis. Steroid therapy may be expected to give good relief. A high degree of eosinophilia also indicates an allergic purpura and one should look for an aetiological diagnosis and it is worthwhile trying the patient on elimination diet. Articles of diet which the patient has been known to be sensitive to, should be withheld during the period of treatment.

Among the steroids prednisone and prednisolone were considered as the most effective in raising the platelet count, the dose being 30 to 100 mg a day.

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## THYROID GLAND

B. B. Mukherji

*Tests of Thyroid Function:* Fraser<sup>1</sup> compared the relative sensitivity of BMR, radio-iodine and protein-bound iodine tests to increased and decreased thyroid function. The best index to severity is given by BMR but there is some overlap over the normal by both the abnormal groups. The radio-iodine test, in the absence of previous medication is the best for suspected thyrotoxicosis. Some nontoxic goitres, however, show similarly high uptakes by this test and in mild myxoedema, the normal range is overlapped even more on the radio-iodine test than on either of the others. Estimation of protein-bound iodine in plasma distinguishes most cases of thyrotoxicosis and stands out the best of the three tests for diagnosis of myxoedema.

Lamberg et al<sup>2</sup> studied serum protein-bound iodine as a diagnostic aid in determination of the thyroid function in 450 individuals suffering from thyrotoxicosis, hypothyroidism, nontoxic goitre, various disorders without evidence of thyroid disturbance and this group also contained 25 healthy controls. The authors found that though there was some unpredictable variation in values ascertained at intervals of a few weeks in the same individual and there was some overlapping of diagnostic ranges, estimation of serum PBI was a valuable laboratory aid in diagnosis of thyroid function.

*Thyrotoxicosis—Carbimazole:* Burrell et al<sup>3</sup> surveyed 1046 patients treated with carbimazole for a mean duration of 9.2 months and found that 0.5 per cent developed major toxic effects such as serious depression of some blood-forming tissue or drug fever and 1.5 per cent minor toxic symptoms such as transient rashes, nausea, vomiting, headaches, etc. All these reactions occurred within the first 2 months of administration and none occurred on a dosage of less than 20 mg a day. The incidence of toxicity was found much lower than that of other antithyroid drugs (major toxic reactions of other antithyroid drugs: methyl thiouracil—9.2 per cent, thiouracil—5.4 per cent, methimazole—1.45 per cent, propyl thiouracil—0.9 per cent). The toxic effects of carbimazole could be readily recognized and controlled.

Burrell<sup>4</sup> recorded a fatal case of marrow aplasia since he reported the above survey with his associates. This is the seventh case of serious marrow depression following carbimazole of which two had been fatal.

Greene and Morgan<sup>5</sup> compared the toxicity of carbimazole with that of methyl thiouracil. 181 consecutive patients needing antithyroid drugs were treated with carbimazole, 10 mg 3 times a day, as the sole therapy in 32 cases, preliminary to radio-iodine in 17 and in preparation for thyroidectomy in 132. Toxic effects were noted in 8 patients, four of which had harmless skin rash and did not necessitate a change of treatment, in 2 purpura (one with psychotic depression and one with sore throat and pyrexia), one pretibial myxoedema and one anaemia. No death was recorded.

## Thyroid Gland

*Treatment of Thyrotoxicosis with Radioactive Iodine:* Clerk and Rule<sup>6</sup> reported the result of treatment and adequate follow-up of 628 thyrotoxic patients with radioactive iodine. As the result of treatment, 82 per cent became euthyroid and the remainder showed varying degrees of hypothyroidism. Recurrence was noted in 0.5 to 1 per cent of cases. Beierwaltes and Johnson<sup>7</sup> treated 330 patients with radioactive iodine. Seventy-one per cent of cases with toxic nodular goitre and 78 per cent with diffuse thyrotoxicosis became euthyroid at the time of the final follow-up. Results of treatment of thyrotoxicosis with radioactive iodine have also been reported in recent years by Macgregor<sup>8</sup> in 150 cases, Bloomfield et al<sup>9</sup> in 140 cases and Hamwi and Goldberg<sup>10</sup> in 133 cases. The general consensus of opinion regarding the indications for treatment of thyrotoxicosis with radioactive iodine are, (a) uncomplicated thyrotoxicosis in patients over 40 to 45 years of age. It is not desirable in children owing to the risk of inducing malignant changes. (b) Those who are refractory or hypersensitive to anti-thyroid drugs; (c) when thyroidectomy is contra-indicated or refused; (d) recurrence after thyroidectomy as results after the second operation are poor and the risk of damage to the recurrent laryngeal nerve is great; (e) severe exophthalmos; (f) severe cardiovascular or other disease associated with thyroid disorder. The only important contra-indication is pregnancy particularly after the 14th week when there is the real risk of foetal thyroid taking up radioactive iodine and receiving direct damage. Side effects are occasional slight tenderness in the gland in the first week of radioactive iodine therapy and sometimes a sense of constriction in the neck 4 to 5 weeks later. Mild exacerbations of thyrotoxicosis following the I<sup>131</sup> treatment are noted from time to time and few fatal incidents of thyroid crises following such treatment have been recorded by Nelson et al<sup>11</sup> and Feitelberg et al<sup>12</sup>.

### Hypothyroidism

*Myxoedema Coma:* Malden<sup>13</sup> reported four cases of hypothermic coma in myxoedema. Extreme dry coldness of the skin was a very striking feature. Three of these cases proved fatal. The fourth patient who recovered was treated with l-thyroxine sodium and corticotrophin and was kept wrapped in electric blankets. One of Malden's cases showed at autopsy the features of Hashimoto's disease. A similar pathological picture was noted in the cases of myxoedema coma reported by Reid<sup>14</sup> and Karhausen and Zylberszac<sup>15</sup>. Marshall and McCaughey<sup>16</sup> described a case of hypothermic myxoedema coma with muscle damage and acute renal tubular necrosis. The authors believe that exposure to cold was a precipitating factor in the onset of coma because all published cases of hypothermic myxoedema coma had been hospitalized in winter. The acute tubular necrosis of kidneys resembling the findings in crush anuria may be due to depressed renal function with hypothermia. Dyson and Wood<sup>17</sup> reported a case of myxoedema coma (which proved fatal on the 5th day) in which tri-iodothyronine was found to be therapeutically potent. The authors recommend tri-iodothyronine as a potent therapeutic agent meriting further trial in the treatment of myxoedema coma.

*Metabolic Insufficiency:* A syndrome of metabolic insufficiency has been described by Kurland et al<sup>18</sup>. This is characterized by a lowered BMR but normal I<sup>131</sup> uptake, serum protein-bound iodine and blood cholesterol level. The patient complains of lethargy, easy fatigability, nervousness, irritability, emotional instability, sensitivity to cold, headache, vague skeletal pain, impaired potency in males and menstrual disturbance in females. Four patients of this group did not respond to thyroid extract or thyroxine but on administration of tri-iodothyronine, the BMR was raised and symptoms were relieved.

### Goitre

*Goitre After Prolonged Ingestion of Iodide:* Turner and Howard<sup>19</sup> reported development of goitre in 13 patients aged 5 to 17 years who had been taking iodide in some form or the other for 2 to 5 years for asthma. Myxoedema was present in seven. Regression in size of the goitre was noted in every case within 8 weeks of institution of therapy with thyroid or sodium l-thyroxine and the thyroid was normal or almost normal on completion of therapy. Excess of iodide in a small number of cases may thus presumably result in diminished production of hormone by the thyroid.

*Recurrent Goitre:* Piercy and Lange<sup>20</sup> reported that of 3500 patients seen at the Thyroid Clinic and Department of Endocrinology of New End Hospital, London, 118 had true recurrences either of goitre or of thyrotoxicosis out of 306 cases referred to as recurrent goitre, having had previous operations for either goitre or thyrotoxicosis. The commonest cause of

recurrence was probably an inadequate initial operation. Most recurrences were due to continued growth of the pathological tissue which remained after the first operation. Factors promoting recurrence were failure to ligate the inferior thyroid arteries and to remove the pyramidal lobe.

**Subacute Non-suppurative Thyroiditis.**—Izah and others<sup>21</sup> have reported six cases of subacute non-suppurative thyroiditis. In 5 of them corticotrophin or cortisone had prompt beneficial effects. The uptake of radioactive iodine in the 5 cases studied was close to zero and returned to normal in the follow-up period of 4 to 14 months. Late recurrence, myxoedema or thyrotoxicosis was not noted in any of these cases. Beneficial effects of cortisone and corticotrophin in the treatment of subacute thyroiditis have also been reported in recent years by Benzamin<sup>22</sup> and Kraft and Wolf<sup>23</sup>.

The aetiology of non-suppurative thyroiditis is unknown. A virus infection has been suggested by Crile, Jr.<sup>24</sup>. Eylan et al<sup>25</sup> have studied 15 cases (14 female and 1 male) of subacute thyroiditis in Israel. Ten of the 11 cases had a positive complement fixation test against mumps virus to a significant titre. A virus, thought to be identical with mumps virus, was isolated from the thyroid gland of 2 of these patients. The authors suggested that mumps virus was the cause of thyroiditis in these cases.

### Analogues of Thyroid Hormone

**Tri-iodothyronine:** Frawley et al<sup>26</sup> studied the response of 14 myxoedematous patients with the following medications: dl-tri-iodothyronine hydrochloride, l-tri-iodothyronine, sodium l-thyroxine and desiccated thyroid. All four substances are effective in the treatment of myxoedema. Tri-iodothyronine acts rapidly and alters the course of myxoedema markedly. It also produces a calorogenic response when the patient is refractory to thyroid extract or thyroxine. The greater potency of tri-iodothyronine may be a disadvantage in the causation of an additional burden on the cardiovascular system. The withdrawal symptoms consisting of weakness, tiredness and recurrence of hypothyroid symptoms, usually appearing within 24 hours of reduction or withdrawal of tri-iodothyronine, may be distressing. To avoid the withdrawal syndrome it is necessary to administer thyroid or thyroxine for several days before the withdrawal. Rawson<sup>27</sup> has noted the following two therapeutic uses of tri-iodothyronine: (1) prompt sobering effect on acute alcoholics; (2) healing effect on chronic radiation changes of the skin.

**Tribromothyronine:** Compston and Pitt-Rivers<sup>28</sup> studied the effects of dl-tribromothyronine in 2 myxoedema patients. It appeared that tribromothyronine had only slightly less activity than thyroxine itself. Lerman<sup>29</sup> studied the response on two patients of myxoedema and found that thyroxine was 2½ times as strong as tribromothyronine on the basis of equivalent weights. Tribromothyronine is therefore a compound of fairly high activity and may be of value when the use of iodine is to be avoided.

**Tri-iodothyroacetic Acid (Triac) and Tetra-iodothyroacetic Acid (Tetrac):** Trotter<sup>30</sup> studied the action of triac in myxoedema as well as euthyroid patients and compared the effects with that of thyroxine. Triac appeared to have relatively greater effect than thyroxine on the blood cholesterol level. He also compared the action of triac with tri-iodothyronine in patients with myxoedema and found that the action of the two drugs was similar but tri-iodothyronine was about 75 times more effective as regards both depression of blood cholesterol and rise of B.M.R. Goolden<sup>31</sup> found that tetrac in dosage no greater than that required for replacement therapy of myxoedema was capable of causing a sizable drop in blood cholesterol of a euthyroid subject. If these compounds specifically lower the blood cholesterol level without inducing hyperthyroidism they might be of value in the prophylaxis and treatment of coronary disease. Lerman and Pitt-Rivers<sup>32</sup> found that triac in a dosage of 7.5 mg daily caused an expected drop in blood cholesterol level with little change in the B.M.R. Larger daily doses however had a cumulative effect on the B.M.R. similar to that of thyroxine.

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## Toxicology of the New Organic Phosphorus Compounds, Some Aspects of

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**TOXAEMIA OF PREGNANCY**—See ECLAMPSIA; PRE-ECLAMPSIA AND PREGNANCY, TOXAEMIA OF

## TOXICOLOGY OF THE NEW ORGANIC PHOSPHORUS COMPOUNDS, SOME ASPECTS OF

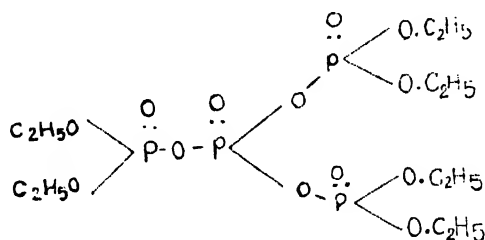
A. R. Natarajan

Introduction of the new organic phosphorus compounds in the field of agriculture, to fight the insect pests is very recent; its existence was hardly known a decade ago. It should be recognised that these insecticides are potent poisons to man and their abuse may result in homicide or suicide. In this article a brief outline on its chemistry, physiological action, toxicology, pathology, prophylaxis and isolation, identification and estimation from the viscera of victims, is mentioned.

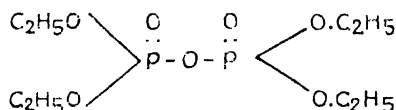
**Chemistry.**—The following synthetic phosphorus compounds are available under different proprietary names.

### 1 Alkyl phosphates

#### 1. H.E.T.P. (hexa-ethyl-tetraphosphate) :



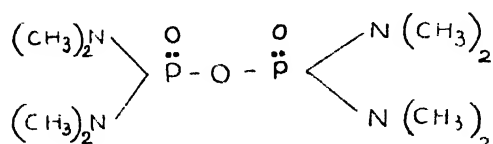
#### 2. T.E.P.P. (tetra-ethyl-pyrophosphate) :



Tetron ; Fosvex

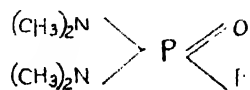
## Toxicology of the New Organic Phosphorus Compounds, Some Aspects of

3. O.M.P.A. (octa-methyl pyrophosphoroamide) :



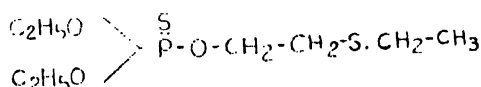
Schradan

4. Dimefox [bis-(dimethyl-amino)-fluoro-phosphine oxide] :



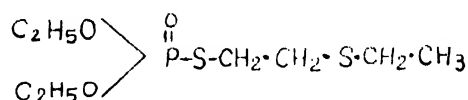
Hanane

5. E 1059 (o. o-diethyl o-ethyl mercapto-ethyl thiophosphate):  
(a) (18 per cent Systox)

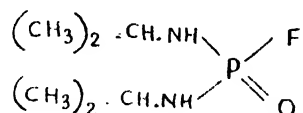


Bayer 8169 ; Demeton

- (b) (30 per cent Isosystox) o. o. diethyl S. ethyl mercapto-ethyl thiophosphate:

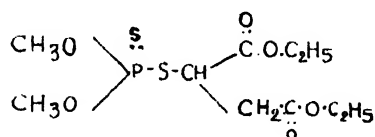


6. Isopestox (bis-isopropyl amino) fluorophosphine oxide:



Pestox 15

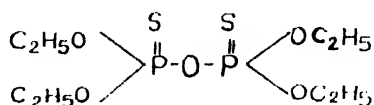
7. Malathion [S-(1-2, dicarbethoxy ethyl)—o.o. dimethyl dithiophosphate]:



Compound 4049

## Toxicology of the New Organic Phosphorus Compounds, Some Aspects of

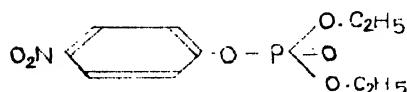
### 8. Sulfotepp (tetra-ethyl o. dithiopyrophosphate) :



Dithione ; ASP. 47

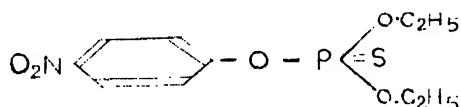
## II. Aryl phosphates

### 1. Para-oxon (diethyl p. nitrophenyl phosphate) :



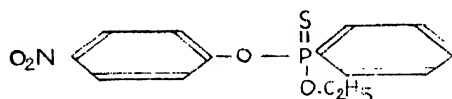
E 600 ; Mintacol

### 2. Parathion (diethyl p. nitrophenyl thiophosphate) :

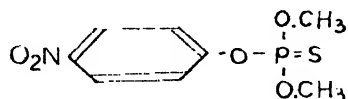


E 605 ; SNP ; Folidol—Bayer

### 3. EPN (o. ethyl o.p. nitrophenyl benzene thiophosphate) :

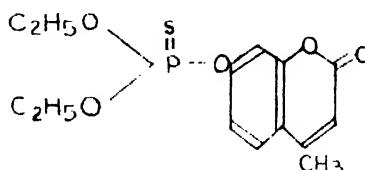


### 4. Methyl parathion (o.o. dimethyl o. nitrophenyl thiophosphate) :



E 605 ; Nitrox

### 5. Methyl unbelliferone o.o. diethyl thiophosphate :



Potasan ; E 838

## Toxicology of the New Organic Phosphorus Compounds, Some Aspects of

All these organic compounds of phosphorus are highly toxic and poisonous to human beings. They are contact poisons and some of them have cumulative effect in the system of the affected person. Their elective site of action is mainly the myoneural junction and the synapse. Chemically they interfere with the enzyme choline esterase and inhibit its action of destroying acetyl choline. They potentiate the cholinergic action of acetyl choline, ultimately giving rise to toxic effects. It would be seen that this physiological action is not very much unlike D.F.P. (di-isopropyl fluorophosphate) which is used in therapeutics for the treatment of myasthenia gravis, paralytic ileus, etc.

Amongst this group of compounds, Parathion is widely used. One single spraying is not very effective. Repeated sprayings produce cumulation and severe toxic effects. It takes time to act but once its action commences, it is invariably successful as far as its toxic action is concerned. In addition it is fat-soluble and is easily absorbed from the skin. Bidstrup has found it to be a cumulative poison.

**Physiology.**—This compound inactivates the enzyme choline esterase; the mechanism is reversible in the early stages but later it becomes irreversible. Bidstrup, Maccance, Callaway et al, Davies and Rutland Corday, Barnes and Davies, and Grob have studied the action of these compounds. They all have reported their effect on the neuromuscular system. The physiology can be broadly discussed under the following heads.

(1) *Muscarine-like Effect*: In the parasympathetic system, on the postganglionic cholinergic fibres. Symptoms and signs are anorexia, nausea, vomiting, abdominal cramps, colic, sweating, salivation, bronchial constriction and cyanosis.

(2) *Nicotine-like Effect*: Stimulation of preganglionic sympathetic fibres and somatic nerves followed by paralysis. Fasciculation and fibrillation of orbicularis oculi, levator palpebrae and the recti muscles of the eyeball.

(3) *Central Nervous System*: Giddiness, restlessness, tremor, insomnia, ataxia, disorientation, coma and death.

(4) *Blood*: Porphyrinuria, chromodacryorrhoea, i.e. flow of red tears due to accumulation of porphyrin in the lachrymal glands.

**Toxicology.**—Signs and symptoms of onset are early and late. *Early*: Giddiness, nausea, anorexia, tightness in the chest and twitching of the eye muscles.

*Late*: Vomiting, sweating, pallor, salivation, twitching of voluntary muscles, delirium, exhaustion, weakness and paralysis of respiratory muscles, coma and death.

These effects last for about 30 hours and fade off in the next 48-72 hours. Sometimes these symptoms may persist for a period of 3 weeks. The choline esterase level in the blood in this period is about 22 to 88 per cent of the normal values of 77 to 142 in the red cells and 41 to 140 in the plasma. Sometimes a 20 to 30 per cent fall is not unusual. There is considerable liver damage as in the case of advanced malnutrition.

**Lethal Posology.**—The most highly toxic of this group is T. E. P. P. and the least is H. E. T. P. A single dose that will produce symptoms of toxicity is 5 mg i. m., or 25 mg orally. The lethal dose is 40 to 45 mg of T. E. P. P. i. m. or i. v., or 100 mg orally (for 70 kg weight). It is observed that Parathion even in very small doses can produce symptoms of severe poisoning. This can be appreciated if it is pointed out that in a field spray regime of eight hours as much as 16 mg may leak through protective clothing and can produce symptoms of poisoning.

**Pathology.**—No macroscopic changes are seen in the tissues. Accumulation of porphyrin in the harderian glands produces pink appearance and in the ultra-violet light bright pinkish red fluorescence.

**Microscopic Appearances**: Mitochondria of the sole plate of the myoneural junction show changes when studied by the Noel and Pomme (1932) technique; precipitating enzyme produce thiocholine as a copper salt. The activity of choline esterase was studied by Koelle and Friedenwald (1949). With the histochemical method suggested by Koelle (1950), deep selective staining at the motor end plate may show evidence of high local choline esterase activity.

As expected there is not much of pathological changes in the tissues. The changes are at enzymatic level leaving the tissues which are outside these, unaffected: it is only transfer and activating mechanisms which are put out of gear and unless studies of the levels of enzymes are



## Toxoplasmosis, Human

made *in vivo*, no evidence of the poisonous effect of the drug can be demonstrated *in vitro*, or in post-mortem examination of tissues.

**Prophylaxis.**—The following general recommendations were made by Zuckerman and his party, to the Ministry of Agriculture, U.K. in 1951, when a conference was convened for the precautions to be observed if these toxic insecticides and weed killers were to be used.

1. Protective clothing: white overalls, coats, aprons, gloves and boots—all made of rubber, eye shields, respirators.
2. Good washing facilities.
3. Working hours: 10 hours' spraying.
4. Efficient supervision.
5. Drinking and eating not permitted during working hours.
6. De-contamination of the machinery and equipment.

**Treatment.**—This is symptomatic: atropine injections are given repeatedly and blood transfusions if necessary. Other supportive measures for shock, exhaustion and restoration of fluid loss are instituted.

**Isolation and Analysis:** It is possible to isolate these compounds from the viscera of suspected fatal cases. A modified Stas-Otto method is adopted. The viscera are acidified with phosphoric acid and the steam distilled. The distillate is extracted with N Hexane. Aliquots are taken and the optical density at 268 M is read off, using a spectrophotometer. Additional checks can be made by hydrolysing it with aqueous potash and after distilling the hexane under reduced pressure, it is diluted and heated at 100 °C for 3 hours when the hydrolysis is complete. The resulting p-nitrophenol is identified by the characteristic absorption spectrum and reading the optical density at 408 mm for quantitative estimation. From the figures obtained the Parathion content can be calculated from a previously calibrated graph prepared from known quantities of Parathion and measuring the optical densities.

**Summary.**—An attempt is made here to cover these organic phosphorus compounds, which are now being used as effective insecticides. Though they are good for the purpose for which they are manufactured and sold, the poisonous nature should neither be lost sight of nor taken lightly. This is a concomitant flaw with all these insecticides. Of late homicides and accidental deaths due to carelessness are on the increase. These compounds after their fatal effects leave little trace of their injurious effects and a post-mortem without chemical analysis gives no clue as to the cause of death.

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## TOXOPLASMOSIS, HUMAN

V. C. Anguli

The first reports of disease caused by *Toxoplasma gondii* described dramatic syndromes in infants. Later it was demonstrated that acquired toxoplasmosis could also be manifested by severe and fatal illness in juveniles and adults. More recently, descriptions of additional syndromes caused by this intracellular protozoan have filled in the spectrum between asymptomatic and fatal infections. Also, manifestations of chronic infections have been described.

Diagnosis of toxoplasmosis must be confirmed by isolation of the parasite or by serologic tests. Since in the acute form of the infection parasites persist in the lymph nodes for long periods, prompt inoculations of material from lymph node into mice should be utilized to demonstrate the aetiological agent. The dye test of Sabin and Feldman and the complement fixation test reveal the presence of two antibodies, the former usually appearing somewhat earlier than the latter. Since there is a high prevalence of positive serologic reactions in the general population, rising titres must be demonstrated in acute cases in order to confirm the diagnosis. The use of both tests is advantageous since, if the dye test shows a stable high titre, the appearance of complement-fixing

antibodies or a rise in their titre is confirmatory evidence of an active infection. In congenital infections, both mother and child should show higher titres ; in the child one must distinguish between active antibodies and passively transferred antibodies, the latter ordinarily decreasing in titre and disappearing after 3 months if the child is not infected.

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168, 1956.

## TRACHEA, BENIGN TUMOURS OF

D. Jagannatha Reddy

Lieutand is said to have reported in 1761 the first case of fibroma of the trachea and this was an incidental necropsy finding. According to the reports of Gilbert et al, primary benign tumours of the trachea are not uncommon in children. These may be fibroma, papilloma or osteochondroma, and often are misdiagnosed as abscess, pneumonia or bronchiectasis which are the usual complications of the growth, but bronchoscopic examination discloses the neoplasm. Gopinath and Betts from Vellore review the pathology and clinical diagnostic features of these new growths and record the findings in a case of fibroma of the trachea successfully treated.

A male patient aged 24, sought medical attention for recurrent attacks of cough. He had dyspnoea on exertion. He was treated for pneumonia six months prior to admission to the hospital. He had tonsillectomy and before that suffered from pneumonia. He developed wheezing and was diagnosed as suffering from asthma. On admission to the hospital, skiagram of the chest showed right basal consolidation ; leucocyte count was 47,000 with 91 per cent neutrophils. He was given the full benefit of massive doses of chemotherapeutic drugs. This was followed by haemoptysis and on relief from the same he was discharged. Again he sought aid for recurrent attacks of pneumonia and bronchoscopy revealed a growth on the right posterolateral wall of the trachea. This was removed and was found to be a fibroma.

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## TRANQUILLIZERS

V. Iswariah

During the recent past, therapeutic armamentarium has been substantially augmented by the addition of a group of drugs designated as "psycho-pharmacological agents." They are distinct from the hypnotics, narcotics, anaesthetics, etc., as the presumed site of action and the scope of utility of the two groups differ.

Psycho-pharmacological agents may roughly be divided into: (1) Hallucinogenics or phantasmagories and, (2) Tranquillizers or ataraxics (ataraxy meaning freedom from confusion and anxiety).

The hallucinogenic agents like *Cannabis indica*, mescaline, etc., that are not new, are more of sociological or toxicological interest. Lysergic acid diethyl amide (LSD 25) derived from ergot, is a recent 'hallucinogenic agent' that lends itself for use as a tool in the hands of experimental psychologist or psychiatrist who seeks to unravel the functions of the brain.

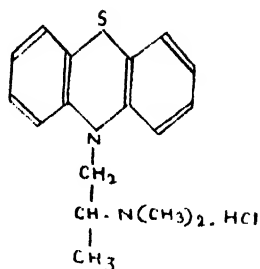
Tranquillizers have been in use for about 5 years ; the outstanding members of the group so far were chlorpromazine and rauwolfia. In subsequent years, a few more synthetic substitutes have been available. The clinical application of these drugs though considerable, is mainly confined to psychotic syndromes.

**Chlorpromazine.**—(Largactil, Thorazine or Megaphen). Though synthesised in 1950 and used for the production of "artificial hibernation" during the next year, its subsequent wide application has provoked a *de novo* study of the compound.

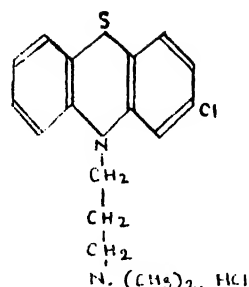
The parent of the compound is phenothiazine which was prepared as a possible chemotherapeutic agent. The amine derivatives of phenothiazine included promethazine, an antihistamine, diethazine or diparcol and ethopropazine or lysivane—of use in parkinsonism,

## Tranquillizers

and chlorpromazine. The chemical structures of promethazine and chlorpromazine are as below:



Promethazine hydrochloride



Chlorpromazine hydrochloride

*Action :* The possible mode of action and therapeutic application of chlorpromazine have been reviewed by several including Dundee<sup>2</sup>, Wilson and Wood<sup>21</sup>, Moyer et al<sup>13</sup> and Robson and Keele<sup>15</sup>.

Though still speculative, it is thought that chlorpromazine exerts a depressant action on the central reticular formation in the brain, which contains numerous synaptic centres that control among others, vomiting, heat regulation, voluntary muscle tone, vasomotor tone and wakefulness. There is also evidence of peripheral ganglion-blocking action<sup>1</sup>. It is also postulated that the depressant action is probably exerted through a biochemical neurohormonal compound, serotonin or 5-hydroxytryptamine (5-HT), which mediates in the synapses<sup>6</sup>. It may be broadly stated that tranquillizers and hallucinogens possess affinity for the same receptor and it seems justifiable to presume that 5-HT is involved here. Chlorpromazine potentiates the effects of cerebral depressants so that smaller doses of central analgesics or general anaesthetics are required; hence chlorpromazine is of use as an anaesthetic adjuvant.

Reference was made to the hypothermic effect of chlorpromazine which action had also lent itself for use as an anaesthetic aid. Normally external cooling provokes vasoconstriction to prevent heat loss, and shivering to help heat production. Chlorpromazine is said to prevent the reaction of the body to extreme cold<sup>1</sup>.

Chlorpromazine may also reduce blood pressure by depressing vasomotor reflexes mediated in the hypothalamus or medulla<sup>3</sup>.

A close similarity between chlorpromazine and dibenamine, an anti-adrenaline agent with reference to cardiovascular effects, has also been noticed by Huidobro<sup>9</sup>. The inhibition of sympathetic tone is traced to an anti-adrenaline action.

Diminished salivary and gastric secretions observed in animals may be due to antagonism between chlorpromazine and acetylcholine (Kopera and Armitage 1954).<sup>11</sup> Though chlorpromazine, a derivative of phenothiazine, has no marked antihistamine action, it shows considerable local anaesthetic action, being more potent and less irritant than promethazine<sup>19</sup>.

*Clinical Uses :* It has to be said that despite enormous experimental data, the use of chlorpromazine in many conditions is still empirical. Some of its uses are as follows :

(1) In general anaesthesia chlorpromazine is fairly extensively used as a premedication (a) for potentiation of general anaesthetics and (b) for 'artificial hibernation', to prevent shock, by facilitating hypothermia.

(2) It is also used to potentiate well-known analgesics like morphine, pethidine, etc., and to enhance the hypnotic action of recognised hypnotics.

(3) It has also been used widely to treat severe vomiting, irrespective of the cause like pregnancy, motion sickness, toxic states, etc. Intractable hiccough has also responded satisfactorily.

In the following conditions, results have not been unequivocal: psychotic excitement, mania, schizophrenia, neurosis, morphine addiction, alcoholism, hallucinations, etc. In aggressive and overactive children, chlorpromazine gives satisfactory results.

A few cases of tetanus have responded to intravenous chlorpromazine<sup>16</sup>.

**Dosage :** In mild mental cases 25-50 mg doses may be administered orally three or four times a day. (Intramuscular injection, unless well diluted is painful). The range of dosage seems to be wide, as 800 mg four times a day for over a fortnight has been tried in some mental hospitals<sup>7</sup>.

For rapid effect 100-200 mg can be given intravenously, well diluted in 200 to 400 c.cm of saline. Duration of chlorpromazine treatment obviously depends on the condition for which it is used ; a few days' treatment may suffice for controlling vomiting, while for neurological disorders, the drug may have to be continued for weeks or even months.

**Toxicity :** Acute—First dose occasionally may provoke alarming reactions like faintness or giddiness presumably due to postural hypotension. This may not be noticed on oral medication. Minor immediate side effects include dryness of mouth, nasal stuffiness and occasional palpitation. Repeated use may not provoke these reactions.

Chronic —Alimentary distress including loss of appetite, nausea and constipation may not be infrequent. Jaundice has been noticed after two to three weeks. The nature of jaundice is not yet clear though it is presumed to be of an obstructive type with or without parenchymatous damage.

A few cases of agranulocytosis following prolonged chlorpromazine therapy have also been reported<sup>18</sup>. There may also be eosinophilia with skin eruptions. Skin reactions seem to be sensitization reactions, e.g. urticaria, erythematous and papular rashes, often more prominent on exposed regions (photosensitization) and occasionally leading to eczema. Contact dermatitis is also possible.

Neurological reactions are sometimes noticed after some months of therapy. Parkinsonism, extrapyramidal lesions, motor restlessness, dystonia, facial grimacing on the one hand and severe form of toxic psychosis on the other, have been noticed.

**Fate :** A dose of 250 mg per kilo orally, raises the blood concentration to the highest level of about 8 mg per litre. In 3 to 7 days only about 7 to 8 per cent of the total intake is excreted, some appearing in conjugated form. It looks as though the rest is metabolised in the body and nothing more is known about it.

**Rauwolfia.**—A revaluation of this ancient Indian medicinal plant has not only revealed its several constituents, but also the possible mode of action of different constituents. Reserpine which is familiar to medical men as a hypotensive agent is mainly a tranquillizer, which should contribute to the hypotensive action. The root (crooked and snakelike, hence the name *serpentina*) contains a complex mixture of alkaloids, resins and perhaps other active principles. The chief among the alkaloids are ajmaline and its derivatives, reserpine, R. S. 51, rescinnamine and canescene<sup>2</sup>. Partially purified alkaloidal mixtures and crude or semi-purified preparations of the root are also available in the market. There appears to be roughly a 1 to 1000 proportion of the dosage of reserpine and the crude root preparations. Vakil (1955)<sup>20</sup> has reviewed the entire literature on rauwolfia.

The two main actions of rauwolfia compounds are the depression of the central nervous system and the hypotensive effect. *The modus operandi* of hypotensive effect is not clear ; the action being delayed, it is not apprehended readily when the crude root preparations are in use. At present there is some confusion with regards to the action of crude extracts, purified total alkaloids, and isolated single alkaloids like reserpine and R.S.51. The hypotensive action of reserpine is of a cumulative nature, being slow and prolonged even after withdrawal. An intravenous injection of reserpine causes a fall in blood pressure after some hours<sup>10</sup>. The fall in blood pressure is accompanied by bradycardia and sedation. Hence sedation and hypotension seem to influence each other beneficially. Plummer et al (1954)<sup>14</sup> hold that most of the effects of reserpine are as a result of restoring sympathetic-parasympathetic balance in the hypothalamus. McQueen et al (1955)<sup>12</sup> are inclined to attribute these effects to a peripheral vasodilator effect in addition to a central sympatholytic action.

The other main action of rauwolfia is depression of the central nervous system. Sedation and not sleep results ; response to afferent stimuli is reduced. A sense of well being, decrease in irritability and improvement in personality are noticed. There may also be relief from headache, fatigue, anxiety, tension and palpitation, if present. Tranquillizing seems therefore, an appropriate term to cover the effects.

## Tranquillizers

Biochemically, reserpine like chlorpromazine, is said to liberate 5-HT<sup>17</sup> with increased excretion of a catabolite of 5-HT viz. 5-hydroxy-indolacetic acid. Confirmation is yet awaited for the finding that reserpine acts mainly through the mediation of 5-HT.

Reserpine however, is deemed to be a drug with a wide margin of safety; while the therapeutic dose ranges from 1 to 5 mg, lethal dose may be in the neighbourhood of 280 mg<sup>18</sup>. For hypotensive action, it could be administered in combination with other hypotensive agents like hexamethonium, pentolinium, hydralazine, etc.

**Toxic Action :** Delayed toxic action is more frequent and this includes mild side effects like nasal stuffiness, increased bowel activity, bradycardia and miosis, all presumably of cholinergic origin. Nightmares and severe mental depression can sometimes be serious, the depression leading to a suicidal tendency. Reserpine has also led to parkinsonism when used in patients with hyperpiesia. Dosage has to be adjusted carefully according to the needs of the patient.

**Allied Psycho-pharmacological Agents.**—*Pacatal* or N-methyl 3-piperidyl 3-methylphenothiazine, is a substitute for chlorpromazine with a claim to be free from the side effects of chlorpromazine. In the recommended dose of 100-600 mg a day, it is often toxic inducing pyrexia, drowsiness, atonia of the gut and bladder, postural dysfunction, etc.

*Benactyzine* (Suavitil) is a hydrochloride of benzilic acid diethyl-aminoethyl ester, said to be useful in anxiety states, tension and in some convulsive disorders and also as a muscle relaxant. The drug possesses anticholinergic properties in addition to the selective action on the hypothalamus. It has to be given in frequent doses to maintain a steady effect. Anxiety states, alcohol addiction, psychogenic asthma and eczema are said to respond favourably, particularly when hysterical and phobic symptoms dominate. It is to be avoided in depressive psychotic states. It is usually administered in 1 mg doses three times a day, gradually increasing to 6 or 8 mg a day. Side effects like palpitation may demand reduction or stoppage of the drug.

*Meproamate*, 2-methyl-2-N-propyl-1, 3-propanediol dicarbamate, in addition to tranquillizing is a potent muscle relaxant acting like mephenesin on neuronal spinal synapses. The duration of action is considerably longer and has been found useful in reducing tension and anxiety, relaxing stiffness and promoting sleep. In frank psychotic conditions it has not proved useful. In doses of 0.4 to 2 g a day, gastric discomfort, drowsiness, muscular weakness and occasional rashes on skin have been noticed.

*Covatin* : This is chemically related to benactyzine, being p-butyl thiodiphenyl methyl-2-dimethylamino ethyl sulphide. It has spasmolytic properties in addition to the properties of benactyzine. Dosage upto 300 mg a day has not shown any serious side effects.

Two new drugs in the psycho-pharmacological series have been available, but it looks as though these are "antidotal" or to "sober" the effects of tranquillizers mentioned above. *Azacyclonol*, *Frenquel*, *Piperadol* or *Meratran* on the one hand and *Ritalin* on the other, are two new compounds said to reverse the effects of tranquillization. They are said to alert and stimulate the C. N. S. without causing euphoria, insomnia, loss of appetite and with no sympathomimetic activity, some of the above being associated with amphetamine. The action of the new drugs depends on the functional level of the brain on which they act i.e., they are more effective in better or higher evolved brain that is momentarily depressed. Available in 1-2 mg tablets, one fears that they are likely to be misused like amphetamine.

The Council of Drugs of the American Medical Association this year (J.A.M.A., 1958, 166, 1040) has given its considered view that the terms "ataraxics" and "tranquillizers" are no longer valid to specify a definite pharmacological action. The state of 'tranquillity' or 'peace of mind' could be achieved by a variety of drugs that can act either as depressants or stimulants of the central nervous system, or by drugs acting purely peripherally. The Council in amplification states that tranquillity could be achieved by (1) non-specific sedation, e.g. alcohol, (2) analgesics e.g. aspirin and morphine, (3) skeletal muscle relaxants, e.g. mephenesin and meproamate, (4) autonomic central suppressants e.g. chlorpromazine and rauwolfia, (5) stimulants of the central nervous system like amphetamine.

The Council decided to abandon the section on "ataraxics" in the new and nonofficial drugs. According to the Council, chlorpromazine and rauwolfia are predominantly central sympathetic suppressants.

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**TUBERCULOSIS OF THE GASTRO-INTESTINAL TRACT**—See GASTRO-INTESTINAL TRACT, TUBERCULOSIS OF

**TUBERCULOSIS OF THE SKIN**—See SKIN TUBERCULOSIS AND ITS RELATION TO PULMONARY TUBERCULOSIS

**TUBERCULOSIS, PELVIC, IN GYNAECOLOGY**

*K. Bhasker Rao*

Pelvic tuberculosis is seen in about one per cent of gynaecological cases. In 70 to 80 per cent, the infection is of extragenital origin and in about 30 per cent there is history of pleural effusion. The natural history of tuberculosis is clearly discussed by Barns<sup>1</sup>, who believes that the primary tuberculous focus (usually pulmonary) heals within 12 months but within this time dissemination occurs elsewhere including the pelvis. The symptoms due to these secondary lesions become manifest in most cases within 3 years from the date of the primary lesion. In every case where the organism has been typed, it has been found to be of the human variety and not bovine. The tubes and endometrium are the common sites of pelvic tuberculosis. The leading symptoms of endometrial tuberculosis, in their order of frequency, are sterility, abdominal pain, menorrhagia, amenorrhoea and leucorrhoea. Endometrial tuberculosis is seen in 5 per cent of all sterility cases ; and in 65 per cent of endometrial tuberculosis tubal blockade is found. This explains the high incidence of sterility or occasional tubal gestations. Treatment consists in B. C. G. inoculation in girls before reaching adolescence to prevent this complication. In any patient with a genital tuberculosis, the primary lesion should be searched elsewhere outside the pelvis especially in the lungs. Treatment is on general lines supported by antituberculous drugs. Streptomycin sulphate one gram intramuscularly daily, and PAS 12 to 20g a day for 12 weeks resulted in a "cure" rate of 69 per cent but 19 per cent recurrence rate in Sutherland's<sup>2</sup> series of 200 cases of endometrial tuberculosis; he obtained better results by substituting PAS by INH 100 mg twice daily for 12 weeks in addition to streptomycin (81 per cent of 53 cases remained negative after treatment). Endometrial biopsy is done at intervals of 3 months for one year and later at intervals of 6-12 months to detect recurrence. Only one abortion but no full term pregnancy has been reported by Sutherland. One case of full term pregnancy a year after treatment for proved endometrial tuberculosis has been reported by Hallum and Thomas<sup>3</sup>. Surgery is rarely done in pelvic tuberculosis except for occasional cases of drug resistance or where the adnexal masses develop or increase in size despite therapy. In cases of menorrhagia or fistulae not responding to conservative therapy, surgery may occasionally be indicated. Whenever necessary, it should be radical.

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**TUBERCULOSIS, PROPHYLAXIS OF**

*M. D. Deshmukh*

Wallgren (1950)<sup>26</sup> states that prophylaxis of tuberculosis has two objects : (1) prevention of tuberculous infection, and (2) prevention of tuberculous disease. Life of a human being,

## **Tuberculosis, Prophylaxis of**

according to him, can be divided into three different periods as far as tuberculosis is concerned.

- (1) Pre-infection period,
- (2) Incubation period,
- (3) Period of latency and of manifest tuberculous disease.

The end of the first period is determined by the occurrence of the first infection. The end of the incubation period is marked by the establishment of tuberculin sensitivity. The pre-infection period is the period of choice for specific vaccination with B. C. G. which he calls "specific dispositional" prophylaxis. Protection from infection by avoiding contact with a tuberculous case is "infection prophylaxis". Strengthening the natural resistance and general health is referred to by him as "unspecific (non-specific) dispositional prophylaxis". This last measure, he states with great emphasis, should begin at birth and end only with death.

The only important addition made in recent years to the above brilliant observation of Wallgren is the idea of chemoprophylaxis or treatment with isoniazid of recently converted tuberculin reactors. This new idea which has been gradually developing in the last three or four years offers an attractive specific measure in the long and uncertain waiting period between infection and disease. The prophylaxis of tuberculosis is discussed under the following headings :

- (1) Prevention of tuberculous infection, divided into, (a) specific vaccination, (b) general measures, and,
- (2) Prevention of tuberculous disease which is divided into, (a) specific chemoprophylaxis, and (b) general measures.

### **Prevention of Tuberculous Infection**

1 (a) *Prevention of tuberculous infection by specific immunization with B. C. G.*: There is a general agreement that B. C. G. is the most suitable form of vaccine to be used for building up specific resistance in uninfected individuals. It is certainly a great tribute to the immortal work of Calmette and Guérin that B. C. G., widely used all over the world today, is derived directly from the parent strain developed at the Pasteur Institute, at the turn of the century.

The controversy over B. C. G. which had raged ever since its first use in human beings by Weill-Hallé in 1921 has now resolved itself into a general agreement about its harmlessness and undoubted efficacy, an understanding of its limitations, and suitability of its application in selected groups of individuals in countries where tuberculosis has been controlled, and advisability of its use on a mass scale in underdeveloped countries (XIVth International Tuberculosis Conference, 1957).

Grunnar Dahlstrom (1954)<sup>5</sup>, gives a good account of B. C. G. with special reference to the valuable contribution of Wallgren to the cause of B. C. G. Shivpuri (1955)<sup>23</sup> has summarized all the evidence of the efficacy of B. C. G. from the results of controlled investigations on animals and man. To this may be added the very recent noteworthy research work in animals by Ström (1955)<sup>24</sup> in Sweden, and Pasquire (1955)<sup>19</sup> in Paris, who used B. C. G. and tubercle bacilli in which radioactive isotopes ( $P^{32}$  in B. C. G.  $C^{14}$  in tubercle bacilli respectively) were incorporated. They have shown that virulent bacilli injected into a previously vaccinated animal are not disseminated so quickly or widely as those injected into a normal unvaccinated animal, proving that vaccination does retard the spread of infection. They have also shown that the vaccinated animal can destroy injected bacilli more rapidly than the unvaccinated animal. This method of investigation (using labelled B. C. G.) has been repeated in man and has given the same results.

Mention must also be made here of the very important results of the investigations carried out by the British Medical Research Council (1956)<sup>2</sup>. In a well controlled clinical trial on 56,700 adolescent boys and girls (between 14½ to 15 years of age), they found after a period of observation of 2 to 2½ years, that the tuberculin negative unvaccinated group showed an annual incidence of tuberculosis of 1.94 per 1000 ; in B. C. G. vaccinated group the incidence was 0.37 per 1000, and in a group vaccinated with Vole bacillus, 0.44 per 1000. Thus both B. C. G. and Vole bacillus vaccine conferred a substantial degree of protection against tuberculosis. There was no case of miliary tuberculosis or tuberculous meningitis in the vaccinated group, whereas in the unvaccinated control group, there were three cases of tuberculous meningitis and three of miliary

tuberculosis. They calculated that if all tuberculin negative individuals had been B. C. G. vaccinated, there would have been a reduction of 55 per cent in the total incidence of tuberculosis for the period of 2½ years. It may be noted that the only complications of the B. C. G. vaccination consisted of occasional regional adenitis and delayed healing of local lesions, while Vole vaccine caused quite a few local lesions resembling lupus vulgaris. Protection by vaccination appears to remain effective upto four years.

Another heartening feature of the protective nature of B. C. G. vaccination is that it continues to be effective even if the vaccinated children are not removed from tuberculous environments (Rosenburg 1, 1954).

There have been only two published authentic case reports (Meyer, 1954<sup>15</sup> and Thrap-Mayer, 1954<sup>26</sup>), where it was proved that death had followed B. C. G. vaccination and a third death in Sweden has been mentioned. The only explanation in these unfortunate cases was that the patients had no inherent resistance to the infection. One can imagine how quickly they would have succumbed to a naturally acquired virulent human infection. It must also be remembered that over 50 million people have been vaccinated all over the world and considering that there were very few deaths and some minor complications like lymph gland enlargement, abscess formation, delayed local healing, lupus, etc., we can safely deduce that of all the active methods of immunizations, B. C. G. inoculation has the least number of complications and hence is the least dangerous. Following the work of Ustvedt on diagnostic use of B. C. G., Heaf (1955)<sup>12</sup> suggested that it was possible to dispense with preliminary tuberculin testing before B. C. G. inoculation, using the vaccine itself for testing sensitivity. An initial injection of 0.01 mg could be given intradermally in the deltoid area and if no reaction occurred in seventy-two hours, a vaccination dose of 0.1 mg could be given in the same area.

It may be mentioned that B. C. G. injected in persons with healed or active tubercular lesions causes no harm. Occasionally, constitutional signs like those of tuberculin reactions namely, fever, joint pains, rash and pleural effusion might follow (Gernez-Rieux and others, 1947<sup>20</sup>, Saye 1953<sup>22</sup>; Foley and Parrot 1, 1954).

It has been mentioned before that in countries where tuberculosis is under control, B. C. G. vaccination is recommended only to contacts of tuberculous persons, those employed in the hospitals or clinics, for seamen, adolescents and young adults, immigrants from Irish and Negro stock, and visitors to countries with a high degree of tuberculous infection (Brookes, 1957)<sup>8</sup>.

Heaf (1955)<sup>12</sup> points out that if one tries to immunize a body simultaneously with two different antigens the formation of antibodies to the inferior antigen may be weaker than what it would be if it was used alone and hence small-pox vaccination should be done first, followed three weeks later by B. C. G. vaccination. In India however, because of the rapid conversion rate of children from 'contact families' (Deshmukh et al 1, 1956)<sup>7</sup>, B. C. G. vaccination should be done in the first ten days of life, especially in case of children of tuberculous parents. Heaf<sup>12</sup> also suggests that to diminish the occurrence of local complications, 'newborns' should have B. C. G. in two divided doses in each deltoid region.

B. C. G. should not be inoculated in persons recovering from measles or influenza owing to the depressing effect of the infection on tubercular sensitivity and immunity. The importance of B. C. G. campaign in India and in other economically under-developed countries, as an important measure of tuberculosis control has been stressed again and again by Benjamin<sup>1</sup>. Mohamed Ali (1956)<sup>16</sup> discussed at length, the place of B. C. G. vaccination in the control of tuberculosis in India. Upto the end of 1956, about 80 million persons were tested, out of which 28 million were vaccinated. It is necessary to stress that to make this measure really effective, all the 'new borns' will have to be vaccinated with B. C. G., especially those coming from communities where incidence of tuberculosis is high. Mantoux-negative contacts of tuberculous patients, all adolescents and young adults and young persons entering certain professions like medicine and nursing, hospital employees, sweepers and policemen should have priority for B. C. G. vaccination. It is very necessary that in mass campaigns, the tuberculin positive reactors should not be sent away with the idea that they have nothing to fear from tuberculosis. They should be advised to report for a check-up to the nearest tuberculosis clinic. Those who are vaccinated with B. C. G. should also be asked to take the commonsense precautions of leading a healthy life and report at once if there is delay in the healing of the vaccinated spot or if any other untoward symptoms arise.



## **Tuberculosis, Prophylaxis of**

We may summarize in the words of Wallgren " that B. C. G. is harmless and causes no real discomfort to the individual ; that, the inoculation must be performed in such a way and in such ad ose as to produce tuberculin sensitivity ;

"That, the intracutaneous method of vaccination which was introduced in 1927, has proved to be a thoroughly satisfactory method ;

"That, the immunity produced is only relative but, thanks to the fact that airborne infection is usually slight, it is nevertheless sufficiently strong as a rule, to form a satisfactory protection against the immediate consequences of virulent primary infection ;

"That, the duration of immunity is different in different individuals but usually lasts for 5 years or more ; that the results so far gained with adequately performed B. C. G. vaccination very encouraging where the immunity has had time to develop after the inoculation and where the virulent infection has occurred after the vaccinated individual had acquired sensitivity to tuberculin".

1 (b) *Prevention of Tuberculous Infection by General Measures*: As the results of infection by tubercle bacilli are uncertain, it is obvious that prevention of infection is the most important measure for the preservation of health. Two main sources of infection have to be considered viz. (1) bovine tuberculosis and (2) human source of infection.

Bovine tuberculosis, once common in Western countries, has now almost disappeared. A drastic policy of elimination of tuberculous cattle followed in the United States and Scandinavia and raising of herds free from tuberculosis, as well as pasteurization of milk has led to direct and rapid control of bovine tuberculosis in man. Benjamin (1956)<sup>1</sup> states that there were no authentic case reports of bovine tuberculosis in man in India.

*Human Source of Infection* : The commonest mode of infection is from person to person by droplet infection through cough spray and by inhalation of infected dust. The dangers of indiscriminate coughing and spitting by tuberculous persons thus become obvious. Wearing of masks by those exposed to infection such as persons nursing a tuberculous patient and by sweepers exposed to infected dust is a necessary precaution. Even more important is the training of infectious persons in the control of cough and disposal of sputum in a safe way. A mask should be worn by the patient when he is being attended to. Isolation of every open case of tuberculosis is no longer necessary, as with proper precautions and prolonged use of antibiotic drugs, dangers of infection to others are minimised.

Chronic cases with persistently positive sputum however need special attention. All the available antibiotics should be used including pyrazinamide-isoniazide, a combination which is rather toxic for general use. (Campagna, Calix and Hauser, 1954)<sup>4</sup>. If it is not possible for economic reasons to use the more expensive antibiotics, isoniazid alone should be given over a prolonged period. It has been shown that isoniazid-resistant strains are avirulent and less infectious (XIV International Tuberculosis Conference, 1957).

Proper treatment of all patients, their rehabilitation and financial help to their families are all important measures, but owing to their high cost, these measures can only be introduced by degrees in a poor country like India where sources of national income are limited (Benjamin, 1956)<sup>1</sup>.

The main problem however is detection of early cases before they become infectious. Contact examinations and mass miniature radiological surveys will reveal a large number of cases where disease was not suspected. A practical difficulty however, is to decide the interval between re-examinations. It appears that contact groups which are susceptible (e.g. infants, adolescents and young adults) will have to be examined every three months for a period of two years and then yearly for a period of five years. Industrial workers, hospital employees, school teachers, midwives and those employed in food catering trades, as well as service personnel like seamen, policemen, etc., should have a chest X-ray at the time of entry into the service and every year thereafter.

Routine radiological examinations of all patients attending hospitals have revealed a large number of unsuspected cases even in Western countries. Such an examination is a good preventive measure for the hospital staff (Brookes, 1957)<sup>3</sup>.

### **Prevention of disease after infection**

2 (a) *Chemoprophylaxis* : The idea of using anti-tubercular drugs as soon as infection is discovered without waiting for tuberculous disease to develop has a very sound theoretical basis

(Deshmukh, 1955<sup>6</sup>; Kathareen, Hans-Kang and Hsu, 1956<sup>13</sup>). Primary infection in children, however asymptomatic, needs to be treated because complications like miliary tuberculosis, tuberculous meningitis and progressive primary tuberculosis, take a heavy toll amongst infected children especially in the younger age group (Edith Linclon, 1954)<sup>10</sup>. Apart from this, as Hsu (1956)<sup>13</sup> pointed out, childhood tuberculosis is the fountain-head of adult tuberculosis. Many follow-up studies have shown that tuberculosis in any generation is determined during the early years of life (Dubos, 1956)<sup>9</sup>. Hence, one of the most effective methods of preventing tuberculosis is to attack the disease in infancy and childhood. Deshmukh and others (1957)<sup>4</sup> have shown that in an industrial city like Bombay, tubercularisation of children from contact families is of a very high degree. Under the age of two, 57 per cent from contact families were positive and only 20 per cent from non-contact families. Up to the age of six, 75 per cent of children from contact families showed Mantoux conversion, whereas only 48 per cent from non-contact families were tuberculin positive.

Clearly, B. C. G. would not help these children unless it was given to them soon after birth. Chemoprophylaxis appears to be the only solution in these cases. It is not always possible to detect tuberculin conversion as soon as it takes place, unless some routine method is adopted, as Heaf (1956)<sup>12</sup> has suggested for instance, that the testing should be done in the first, second, fifth, ninth and twelfth years. Health visitors and nurses could be trained to carry out the test. In fact, Volmar (1957) has suggested that mothers should be trained to do yearly testing on their children. Another advantage of early diagnosis of tuberculous children is finding amongst the contacts, infectious persons needing treatment, as children invariably get infected from adults in close contact (Gedde-Dahl, 1952; MacDougal and others, 1952)<sup>11,14</sup>. If chemoprophylaxis is widely adopted and succeeds in its aims, the population of today which carries living virulent tubercle bacilli in the latent form will be replaced by a population in which these organisms have been largely destroyed by the combined effects of natural defence mechanisms and chemotherapy.

Isoniazid is the obvious drug of choice for use in chemoprophylaxis. It is cheap and can be taken by mouth in one or two daily doses. Its action is superior to that of streptomycin or P. A. S., in that it can kill intracellular organisms while it has also the ability of being secreted in serous membranes, which prevents meningitis. The use of a single drug for treatment was at first, objected to by some workers for fear of development of resistant strains, but these fears are allayed by the discovery that isoniazid-resistant strains are biologically changed and are less virulent and so the danger to the host or to the contacts is minimised (XIV International Tuberculosis Conference, 1957). Palmer (1956)<sup>17</sup> conclusively showed the protective power of isoniazid in guinea pigs. Administration of five mg of isoniazid per kg of body weight in drinking water protected the guinea pigs not only from the first challenge by way of injection of live virulent tubercle bacilli but even one month after discontinuance of the drug a second injection of tubercle bacilli was successfully resisted. Robinson (1955)<sup>21</sup> found that six children on isoniazid prophylaxis had shown reversal of tuberculin reaction. Deshmukh and others (1957)<sup>7</sup> found that seven out of seventy-six children showed complete reversal of tuberculin reaction after 6 months of isoniazid treatment. In addition to this a considerable number (47 per cent) showed diminution in the degree of tuberculin reaction. None of the children in the control group showed any diminution or reversal of tuberculin reaction. A small percentage in each group showed increase in the degree of tuberculin reaction, and hence it is unlikely that the reversal was due to the cortisone-like depressing effect of isoniazid on tuberculous allergy. It is probable that reversal of tuberculin reaction after isoniazid means a complete clearing of infection.

Isoniazid prophylaxis is being practised on a large scale in many countries. It will be some time before proper evaluation of this measure can be done. The recommended dose of isoniazid is 5 mg per lb body weight and the duration of treatment has to be at least one year. Application of isoniazid prophylaxis appears to be indicated for the following groups :

1. All recently converted tuberculin reactors, especially those with history of contact with an open case of tuberculosis.
2. All children under three years showing a positive tuberculin reaction with or without history of contact.
3. Adolescents and young adults in contact with an open case of pulmonary tuberculosis.

## Tuberculosis, Prophylaxis of

4. Tuberculin positive children suffering or recovering from infectious fevers.
5. Tuberculin positive children or adults with past history of tuberculosis suffering from diabetes mellitus.
6. Pregnant women with history of pulmonary tuberculosis.
7. Children vaccinated with B. C. G., when there is delay in healing of the vaccination spot or if regional adenitis develops.
8. Children under the age of three who are vaccinated with B. C. G. but have to live with an open case of tuberculosis at home. In these cases isoniazid should be given after tuberculin conversion has taken place.

2 (b) *Prevention of disease after infection by general measures*: In Western countries, where tuberculosis is controlled, the aim is to keep the population free from infection. Palmer (1957)<sup>18</sup> has shown that when such a control of tuberculosis is obtained, tuberculin positive reactors are more likely to yield cases of tuberculosis than those reacting negatively to tuberculin. However, in an economically underdeveloped country like ours, the majority of the population is infected by the time adulthood is reached. The rate of infection is more rapid and higher in those who are in contact with open cases of tuberculosis. Hence, it is all the more important for us to concentrate on measures of preventing disease in those who are infected. We do not yet know all the factors which lead to the development of the disease in infected persons. The result of the first encounter between the bacillus and the body is decided by the inherent resistance and the acquired immunity. We know that there are some races with a low inherent resistance and even in races with high resistance, some families and individuals are found to have low resistance. The degree of immunity seems to fluctuate from time to time and appears to be particularly low in infancy, adolescence and old age. It is also adversely affected by certain factors like measles, influenza and diabetes mellitus, mental and physical fatigue. Hence preventive measures are to take special care at the susceptible ages, to maintain a high standard of health, and to prevent or promptly treat associated diseases. One has to be particularly on the lookout for diabetes mellitus as the incidence of tuberculosis amongst diabetics is very high. Tuberculosis runs an acute course and is more difficult to control among diabetics than in non-diabetic persons. All diabetics should have periodic radiological examination of the chest, and investigations should be done in all tuberculous persons to exclude diabetes. In women, the child-bearing period is to be specially guarded against, especially in the poorer class of people, as it throws a great strain on the individual. Chest screening or X-rays should be a routine in antenatal and postnatal period.

**Summary.**—Although the ultimate control of tuberculosis will be achieved only when the standard of living is raised, poverty, overcrowding, and malnutrition abolished, all practical preventive measures must be vigorously pursued at all times. Establishment of a sufficient number of well-staffed tuberculosis clinics with facilities for diagnosis and treatment, B. C. G. vaccination of the uninfected at an early age, chemoprophylaxis of the infected in susceptible groups and maintenance of a high standard of health are means which are bound to go a long way in checking tuberculosis.

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## ULCERATIVE COLITIS—See COLITIS, ULCERATIVE

## URINARY TRACT INFECTIONS, CHEMOTHERAPY OF

W. R. Bett

The treatment of urinary tract infections is becoming more complicated as the number of sulphonamide—and antibiotic—resistant strains of organisms increases. Fortunately, the introduction of new drugs has so far prevented this from threatening to be an acute problem.

*The Sulphonamides*: In a recent review Herrold described the sulphonamides—Gantrisin, Elkosin, and Thiosulfil as useful additions to the urologist's armamentarium because of their few side effects. According to Terrell and his collaborators, sulphadiazine and sodium sulphadiazine, given by mouth, are capable of producing sustained effective blood levels, but they have the disadvantage of a high incidence of renal tubular irritation and precipitation in acid urine. Sulphonamide combinations have significantly reduced the risk of crystal formation. In their opinion, the first two agents of choice are sulphadiazine and sulphamerazine. Sulphamethazine has been widely used as the third component. More recently Elkosin has been compared favourably with the other sulphonamides.

The relative efficacy of Gantrisin and of a triple sulphonamide mixture (sulphadiazine, sulphamerazine and sulphamethazine) was tested by Bunn and his co-workers in 54 patients with various urinary tract infections caused by 99 different pathogenic organisms. Neither preparation proved superior to the other. In routine treatment the sulphonamides are to be preferred to the broad-spectrum antibiotics on the grounds of 'safety, convenience, cost, broad antibacterial activity, and the observation that serious intestinal floral changes do not occur with their administration.'

Acetyl Gantrisin, 0.5 g four times daily, was administered by Garvey and Strawcutter to 100 patients with infections of the urinary tract. Cure or satisfactory relief was obtained in 91 per cent. The drug proved effective against coliform bacilli, proteus (in 8 of 9 cases), aerobacter, pseudomonas (4 of 5), alkaligenes, streptococcus faecalis, and haemolytic and non-haemolytic staphylococci. Febrile drug reactions occurred in two patients.

*Antibiotics*: Polymyxin B, which is given parenterally, concurrently with oral Terramycin or Aureomycin, is one of the few drugs effective against pseudomonas infections. The nephrotoxic factor, however, warns Herrold, demands that it be used with great care. Cycloserine has the advantage that it can be given for long periods. It is useful in the treatment of tuberculosis and in trichomonas infections of the urethra and prostate, but is ineffective against pseudomonas, proteus, and streptococcus faecalis. In Herrold's experience, these organisms are best treated by the following combinations of drugs:

Chlortetracycline and streptomycin for pseudomonas.

Streptomycin and chloramphenicol for proteus.

Streptomycin and penicillin for streptococcus faecalis.

Carroll (1955) considers erythromycin to be the drug of choice for staphylococcal infections. High blood levels cannot be attained with oxytetracycline or chlortetracycline, whose action

## Urinary Tract Infections, Chemotherapy of

is bacteriostatic rather than bactericidal. The emergence of resistant strains has increased the incidence of proteus and pseudomonas infections. The best drugs available for proteus infections are, in his opinion, nitrofurantoin, chloramphenicol, and acetyl gantrisin. As pseudomonas is resistant to most drugs except polymyxin B which is highly nephrotoxic, infections due to these organisms present a special problem. Carroll recommends a combination of streptomycin and oxytetracycline as the best treatment.

**Nitrofurantoin :** Nitrofurantoin (Furadantin) is a substituted furan derivative having a nitro group at the 5-position in the furan ring. It is the first of this series to be given by mouth for the treatment of urinary tract infections. Its bacteriology, pharmacology, toxicology, and therapeutic uses have recently been reviewed by Bett and by Fairbrother.

Schneerson carried out sensitivity tests with 1013 bacterial strains belonging to a number of species obtained from various sources. With the exception of 56 out of 101 strains of *Pseudomonas aeruginosa* and 3 out of 281 strains of *Escherichia coli*, all were susceptible to the level of nitrofurantoin reached in the urine (400  $\mu\text{g/ml}$ ). The effect on *Proteus vulgaris* and *Micrococcus pyogenes* var. *aureus* was particularly noteworthy in view of the high degree of resistance shown to the antibiotics used at the present time.

Stewart and Rowe found nitrofurantoin effective within 8 to 36 hours against infections due to *Escherichia coli*, *Aerobacter aerogenes*, *Proteus rettgeri*, and *Proteus morganii*. Given with carbacol (Doryl), it proved singularly effective in neurogenic bladder infections. Side effects were noted in less than 10 per cent of patients, less than 1 per cent being severe. Carroll (1957) describes nitrofurantoin as 'by far the best drug' in the treatment of infections due to proteus.

Richards and his colleagues obtained favourable clinical results in the great majority of 39 patients with acute and uncomplicated urinary tract infections. *In vitro* studies showed the action of the drug to be primarily bacteriostatic, though at higher concentrations it has a bactericidal effect on the more susceptible strains. According to an editorial comment in the *Year Book of Urology* 1955-56, the action of the drug appears to be bactericidal rather than bacteriostatic. Extensive clinical and laboratory investigations have shown that the danger of damage to the seminiferous tubules of the testis is 'non-existent or extremely insignificant'.

Carroll and his co-workers report that clinically valuable blood levels were obtained if an initial dose of 200 mg of nitrofurantoin was given. If this was followed by the administration of 100 mg every six hours, satisfactory levels could be maintained for at least three days. The drug effectively controlled infections due to *Escherichia coli*, *Aerobacter aerogenes*, *Proteus vulgaris*, *alkaligenes faecalis*, enterococci, and staphylococci. *In vitro* studies of 94 strains of proteus showed that 84 were sensitive to nitrofurantoin; 21 of 25 patients with proteus infections were controlled by the drug.

It is interesting to note that, while frequently ineffective *in vitro* against pseudomonas, in several reported clinical trials nitrofurantoin proved much more active than might have been expected from *in vitro* sensitivity tests.

**Non-gonococcal Urethritis :** Trials with the antibiotic spiramycin indicate that it is of value in the treatment of non-gonococcal urethritis. Willcox treated 41 patients of whom 36 could be followed up. All but 8 of these were cured. No serious toxic reactions were noted. Mild side-effects in 8 patients included diarrhoea, nausea, rash, rectal soreness, and pruritus. The results obtained with spiramycin were comparable with those following the use of the tetracycline antibiotics and with erythromycin, and were markedly superior to the results achieved with streptomycin, the sulphonamides, penicillin, and chloramphenicol.

**Trichomoniasis :** Reports on the use of tritheon (2-acetyl-amino-5-nitrothiazole) in the treatment of male and female trichomoniasis are encouraging. Of 188 women treated by Perl and his colleagues, one course sufficed in 104, two courses in 59, three in 20, and four in 5. Negative cultures were obtained in 94 patients: in 16 of 28 men after one course of treatment, and in 2 after a second course. This eradication of the organism in the male is particularly interesting.

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## URINARY TRACT, RADIOLOGICAL ASPECTS OF THE--See GENITO-URINARY TRACT, RADIOLOGICAL ASPECTS OF

### UTERUS, RUPTURE OF THE

*K. Bhasker Rao*

Gross abnormalities are rarely seen as cause of the rupture of the uterus at present: most of the cases occur due to yielding of the previous scar. In a large group of patients, there may not be any apparent cause found. It cannot be stressed sufficiently that the classical caesarean and classical hysterotomy should be avoided in any patient. In a large series of previous caesarean operations, Dewhurst found that only 0.4 per cent of the lower segment scar yielded during subsequent labour whereas 6 per cent of the classical scars ruptured during the following pregnancy or labour. According to him the chance of a lower segment scar rupturing if a patient is allowed to go into labour is 1 in 122. In 11 out of 13 cases where the lower segment scar yielded, the diagnosis was made only on laparotomy. The general condition of the patient remains good though she may have tenderness over the scar. The pains persist and over the suprapubic region the foetal parts may be felt more easily, occasionally there may be haematuria, but in every case the mother survives and the foetus is saved as it is still inside the uterus. After classical caesarean, rupture is dramatic with severe signs of shock and a heavy foetal mortality. Spontaneous rupture may be seen in multiparas beyond the fifth, often without any obvious cause. The head may be even on the pelvic floor and therefore may not recede with the rupture, as it occurred in 4 out of 10 cases reported by Corbett. There may not be any vaginal bleeding if the presenting part is fixed. Unexplained sudden foetal death, localised pain, rise in pulse rate, haematuria or persistent postpartum haemorrhage after a difficult delivery should make one think of this complication so as to discover and treat these cases early.

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### VENEREAL DISEASES—See SKIN AND VENEREAL DISEASES

### VENEREAL DISEASES IN GYNAECOLOGY

*K. S. Krishnan*

**Rectal Gonorrhoea in Women.**—Interest in the subject has been revived. Jenson says that isolated rectal gonorrhoea in women is relatively rare and is nearly always combined with urethral, cervical or urethrocervical gonorrhoea. This, according to him, suggests that in the isolated infection peno-anal coitus—as an anticonceptual measure rather than a sexual perversion—has been performed intermittently with normal coitus. Pelozé (1939) quoted by Jenson, refers to the anatomic-histological conditions, namely, length of the anal canal with stratified squamous epithelium and tonic contraction of the sphincters which refute the theory

## Venereal Diseases in Gynaecology

of proximity between the vagina and anus in the pathogenesis. He cannot explain the rectal infection except by the assumption that it is due to infected instruments, explorative finger stalls, irrigating nozzles, etc. The comparatively more frequent occurrence of gonorrhoeal proctitis has assumed a significance in the penicillin era. Jensen points out that the very large bacterial flora of the rectum capable of forming penicillinase which destroys penicillin might compromise this antibiotic therapy. Clinical support for this assumption has been found in the account of the effect of penicillin therapy on female gonorrhoea published from the St. Gorans Sjukhus, Stockholm, which shows that not less than 60 per cent of women admitted with anorectal gonorrhoea had a relapse after penicillin therapy (3000 I. U. procaine penicillin) while the percentage of relapse for the entire material (including cases of proctitis) was only 15 per cent.

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**Cyst of the Skene's Gland.**—Hainsworth reports a case of cyst of the Skene's gland. References in literature are very occasional. Shaw (1954) is quoted as saying that while cysts of Gaertner's duct are fairly common, most authorities agree that cysts of the Skene's gland are very rarely seen. Legault of Montreal described one case of his, a multiparous woman of 36, who complained of some frequency of micturition with constitutional symptoms often for 2 years after the birth of her 5th child. The cyst was of the size of a large olive and contained greenish yellow, sebaceous material which unfortunately was not cultured. The cyst was easily excised surgically. He discussed fully the differential diagnosis from urethral abscess, polyp, carcinoma, urethral prolapse, diverticulum, calculus and herniation into the urethra of a cystic dilatation of the lower end of the ureter. A cyst of the gland of Skene shows as a small swelling about  $\frac{1}{2}$  to 1 inch (1.25 to 2.5 cm) in diameter, in or just beside the midline, between the mouth of the external urinary meatus and the vaginal opening, producing a bulging of the anterior vaginal wall. The cyst is symptomless until infection occurs in it and it is apparent that no difficulty in diagnosis should be found. In the case reported in the present paper the causative organism traced was *Staphylococcus aureus* and its method of spread was easily followed. It has to be remarked that Novak and Novak (1952) mention that the gonococcus is the usual organism.

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**Treatment of Condyloma Accuminatum in Pregnancy.**—Condyloma accuminatum is caused by contamination of the vulva and is often engendered by a prolonged, irritating and neglected vaginal discharge, frequently that from gonorrhoea. During pregnancy the lesions will usually hypertrophy and form large cauliflower-like masses in the vagina that may obstruct delivery. Rarely does malignant degeneration occur. Anthony C. Milea illustrates these points reporting a case of a large obstructive vulval lesion of condyloma accuminata in a young multipara successfully treated at 6½ months' gestation, by local application of 20 per cent Tr. podophyllin and intramuscular penicillin. Lesions generally cleared permitting uneventful pelvic delivery.

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**Granuloma Inguinale.**—Watsford and Alderman discussing granuloma inguinale point out that the lesion starts as small ulcerated areas with a smooth shining base on the inner surface of the labia. The ulcers may become deep, extend upwards and backwards spreading to the anal margin involving the perineum and then into the upper parts of the thighs. Scarring and pseudo-elephantiasis are produced. The scar tissue breaks down and new ulcers are formed which heal again and break down. Complications are very pronounced. Scarring around the vulva interferes with child-birth and in one of the authors' cases, held up labour for some hours. Aureomycin is recommended as the drug of choice by Zigas. In the experience of the authors streptomycin has given good results, the lesions healing rapidly.

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**Antibiotic and Chemotherapeutic Agents.**— Jones et al discuss the role of antibiotics and warn against the danger of allergic and anaphylactic reactions that may occur, and of the disturbance of the normal flora of the bowel by oral tetracycline compounds, of the blood dyscrasias that may arise from chloramphenicol, of the 8th nerve damage from streptomycin, of renal damage from bacitracin and of renal and nervous system damage from polymyxin B. Mentioning the long acting repository penicillins as agents of choice they point out the usefulness of Bicillin, 2,400,000 units in syphilis as a single injection in the first and second trimesters. Gonorrhoea is treated with 300,000 units procaine penicillin G intramuscularly daily for 2 days. Lymphopathia venereum is treated with 1 gm sulphadiazine q.d.s. for 10 to 15 days. Granuloma inguinale is treated with one of the tetracyclines or chloramphenicol 500 mg orally q.d.s. for 10 to 15 days.

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**Trichomonas vaginalis Infection.**—In spite of the numerous publications on the subject and the discovery of many trichomonocidal drugs and treatment routines, cent per cent eradication of the infection in some cases is a goal yet to be reached. *T. vaginalis* considered at one time to be a harmless commensal is now known to be an important pathogen causing a very troublesome vaginal discharge. Coutts and others (Urologic and Antivenereal Polyclinic, Chile) have made a significant contribution towards the understanding of the pathogenesis of the organism. They consider, "In recent years, fungi, viruses, spirochaetes and protozoa have tended to displace the gonococcus in the causation of acute and chronic inflammation of the lower genito-urinary tract in both sexes and for this reason more examples of such infection are now seen at the urological clinics". It is thought that the use of antibiotics and newer drugs have created this problem. In the words of the well-known pathologist Boyd, "Unfortunately new lesions and new diseases have appeared in the wake of the great wave of successful therapy. Chemotherapy and hormonotherapy are only superficially an unalloyed blessing, for, while solving some problems they help to create new ones. It must not be forgotten that what is powerful for good can also be potent for evil". Coutts et al demonstrated *T. vaginalis* in 1690 out of their 2482 cases of non-gonococcal urethritis. It is not mentioned how many were females. Hees has been quoted as having cultured *T. vaginalis* from the blood of infected women. This fact has caused consternation among some venerologists. Davies believes that the parasite may enter the vagina via contaminated water, since many of his patients gave a history of infection which could be traced to seasons when they were bathing in warm, still, algae-ridden inland waters. Krishnan commends this aspect of the aetiology to Indian research workers as a fruitful field for investigation because there are many algae-ridden tanks and river springs in which men and women bathe everyday irrespective of the seasons of the year. In river springs, especially, a large number of people bathe in a comparatively small collection of water.

**Post-menopausal Trichomonas Vaginitis :** Numerous publications on *Trichomonas vaginalis* infection in women have appeared, but scant mention has been made of the occurrence of the flagellate in patients of menopausal and post-menopausal age. In a survey of 859 women in various age groups, however, Feo found 65 patients harbouring *Trichomonas vaginalis* among 504 aged between 50 and 91 years. Of the 65 positives, 24 were beyond 60 years of age. Attention is drawn to the comparatively mild symptomatology. Evidence is presented in support of a theory that the implantation and survival of *Trichomonas vaginalis* in the vagina are the result of the serum present. The reader is reminded about the incidence of infection in relation to menstruation. The role played by the oestrogens in the aetiology of *T. vaginalis* vaginitis is a moot subject. Chappaz and others refute the theory that oestrogens play a role in the pathogenesis of the infection. To support their belief they have observed the premenstrual cyclic appearance of the trichomonads, a low karyo-pyknotic index in stained vaginal smears and the frequency of infection in patients with ovarian disease. Feo's study seems to substantiate further the latter premise. *T. vaginalis* was found in patients well beyond the menopause and in a state of marked hypo-oestrogenism. The flagellate survived the environmental conditions of the resulting atrophic vaginal mucous membrane especially the serum transudate, with or without a superadded inflammatory exudate. It has to be remembered that serum or whole blood is an



## Venous System, Vertebral, and its Connections, Anatomy of

essential ingredient of every successful culture preparation. The organism itself gives off a toxic substance which causes degeneration of epithelial cells. The author has drawn his conclusions after extensive investigations which included vaginal biopsies and hormonal assays.

**Treatment of *T. vaginalis* Infection:** Among the recent trichomonicides, "carlendacide" and "Lautric" deserve mention. Carl H. Davis and Grand, after experimenting on many compounds, found a compound which they named carlendacide (trade name Vagesec) which is a balanced blend of polyoxyethylene nonyl phenol, ethylene diamine tetra-acetate and doctyl sodium sulpho-succinate. It dissolves mucus, fat and blood clot and kills trichomonads in the vaginal canal in the matter of a few seconds. The vaginal canal is dried and is thoroughly swabbed with 1:250 v/v aq. solution of carlendacide. After three minutes the canal is dried and the patient sent home without any packing. Three such treatments are given in the first week, two in the second and one in the third. Meanwhile, the patient takes one or two carlendacide douches a day (one teaspoonful to the pint) on the days she does not visit the doctor's clinic. The husband is advised to retract and wash his prepuce daily and after coitus with 1:500 v/v carlendacide solution. It is mentioned that the drug quickly inactivates sperm cells. When pregnancy is desired this drug should not be used.

Clifford gives the results of treatment of 100 cases (with 100 per cent follow-up) treated with "Lautric", a simple and inexpensive trichomonicide, (supplied by Mr. T. D. Williams, President, Gynaecological Specialities Inc., East Alton, Ill.). The chemical formula is  $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{O}\text{SO}_4\text{Na}$  plus 1 per cent sodium propionate. Lautric used properly as a douche (paste also being available) is claimed to have cured 92 per cent of the patients in the series, 8 being total failures. 72 per cent of the 32 pregnant patients were cured. No toxic or allergic manifestations were encountered.

Pearson treated 23 patients, with a one year follow-up, inserting a 100 mg Terramycin pessary high up in the vagina, night and morning, for 40 consecutive days during which time sexual intercourse and douching were forbidden and treatment continued throughout the menstrual period. The results showed that the use of Terramycin pessaries in the treatment of trichomonas vaginitis gave no better result than methods of treatment in current use.

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## VENOUS SYSTEM, VERTEBRAL, AND ITS CONNECTIONS, ANATOMY OF

S. L. Robert

The subject of the vertebral venous system has of late come into a great deal of prominence and although there still remain a few points of controversy, much new knowledge has been added with the result that the overall picture now stands much better defined than in the past. This venous system according to Johnston and Whillis<sup>9</sup> consists of:

1. Intricate plexuses along the entire length of the vertebral column divisible into:
  - (a) An internal plexus inside the vertebral canal which lies between the dura mater and the vertebrae and forms anterior and posterior internal plexuses opposite each vertebra which by longitudinal linkage form four longitudinal veins or sinuses—two in front and two behind. At the upper end these plexuses are connected with the occipital and sigmoid sinuses, the network of basilar sinuses and with the anterior and posterior condylar emissary veins.
  - (b) An external plexus surrounding the vertebral column also divisible into anterior and posterior plexuses which anastomose freely with each other and with the internal plexus.
2. Basivertebral veins which drain the vertebral bodies, emerge from the foramina on their posterior surfaces and open by valved orifices into the transverse branches uniting the anterior internal vertebral plexuses. They become enlarged in advanced age.
3. Intervertebral veins which accompany spinal nerves through the intervertebral foramina. They receive veins from the spinal cord, drain the internal and external vertebral plexuses

and end in the vertebral, posterior intercostal, lumbar and lateral sacral veins, their orifices being provided with valves. Some of the posterior intercostal and lumbar veins drain into the azygos vein. Tributaries to the azygos vein are provided with complete valves.

While the above description mentions a number of valves, Grant<sup>6</sup> states that the vertebral canal contains a deep plexus of thin walled valveless veins. Hollinshead<sup>7</sup> also states that all the vertebral plexuses are drained in part through the lumbar veins and since neither the lumbar veins nor the vertebral venous plexuses are provided with valves, blood may under proper conditions of pressure pass in either direction. He further says that the lumbar veins are usually described as entering the inferior vena cava but have a highly varying pattern. They are commonly more or less united by an ascending lumbar vein which may also anastomose at its lower end with the common or internal iliac vein and a presacral plexus of veins including the median sacral vein and contribute above to the formation of azygos and hemiazygos veins and on the left but not on the right side may have connections to the renal vein<sup>1</sup>.

Besides the function of returning the venous blood from the spinal region, the possibility of the role of the vertebral venous system as one of the collateral channels in cases of obstruction of the inferior vena cava has been recognized since a long time. Jelfcoate<sup>8</sup> says that it is now generally accepted that the lumbar veins serve as one of the main routes for blood when the inferior vena cava is obstructed in man and he further adds that the vertebral venous system provides a theoretical pathway from the pelvis to other parts of the body which is not interrupted by the lung.

Apart from the above functions the possibility of the role of the vertebral venous system in the spread of malignant deposits in the spine has recently focussed the attention of several workers on this subject. Their studies of the spread of metastases in the spine and their experiments carried out to understand and explain them have not only yielded much fruitful information on this topic but have also thrown much new light on the question of functions as well as connections of the vertebral venous system. In this connection Batson's<sup>2</sup> studies stand out as having contributed a good deal to the new knowledge and new concepts about this venous system. Grant<sup>6</sup> says that Batson on the basis of his work was led to add to the recognized pulmonary, portal and caval venous systems a fourth or the vertebral venous system. This comprises the veins of the brain, skull, viscera, vertebral column (and their valveless connections in the limb girdles) and the veins of the body wall. Grant after describing Batson's experiments says that they indicate:

1. that compression of thorax and abdomen with the larynx and other sphincters closed as occurs in straining, coughing and lifting with the upper limbs not only prevents blood from entering the thoraco-abdominal veins but squeezes it out of them into the vertebral system;
2. that the increase in the intraspinal and intracranial pressure that occurs during coughing, sneezing and straining is active, not passive;
3. that tumours and abscesses having connections with the venous system may have metastases anywhere along this system without involving the portal, pulmonary or caval systems and,
4. that the cranial and spinal parts of the system as well as being pathways are blood depots or storage lakes of blood; further,
5. they reveal the channels through which blood from the lower limbs and pelvis may in favourable circumstances return to the heart after the inferior vena cava has been obstructed below the renal veins.

Hollinshead<sup>7</sup> also quoting Batson states that it is through the lumbar and vertebral plexus of veins and similar ones in the pelvis that metastatic involvement of the vertebral column or even of the brain itself may occur.

Johnstone<sup>10</sup> from his experimental studies came to the conclusion that the principal venous drainage from the prostatic plexus flows into the caval system but that free communication exists with the paravertebral veins. Referring to spread of malignant growth, he concluded that while some cells may be disseminated along the vertebral venous plexus, there was no definite proof that these vessels provided the main route for the spread of metastases in carcinoma of the prostate, breast and bronchus.

## Venous System, Vertebral, and its Connections, Anatomy of

Willis<sup>11</sup>, commenting on Batson's view that the vertebral venous plexus is the major pathway by which prostatic and other tumours disseminate to the axial skeleton states that it is quite possible that after the establishment of spinal metastases and the collateral diversion of blood flow occasioned by their occlusion of vertebral veins it may be a route of local spread but that there is no reason to suppose that remote metastases develop in this way rather than by the usual route of dissemination via the lungs.

Franks<sup>\*</sup> (1953)<sup>4</sup> work on the other hand has supported Batson's view that if the inferior vena cava is obstructed in life by increased intra-abdominal pressure due to straining, coughing, etc. the blood flow may be diverted into the vertebral venous system carrying with it tumour or other emboli. He however went on to state that in prostatic carcinoma, while the spread of minute emboli having reached the lungs in the caval circulation and their being passed on through the systemic arteries to the bones must remain a possibility, the presence of large vascular channels with direct communication between the prostate and bones by-passing the pulmonary circulation makes this a much more probable route. He also confirmed by injection methods a direct communication between the prostatic veins, the vertebral venous system and the veins of the pelvic bones.

Bowsher<sup>3</sup> after his extensive studies of the azygos venous system in man and animals states that the azygos venous system is the main intermediary between the superior caval system and the internal vertebral venous system. He stresses the fact that the azygos venous system is functionally a part of the internal venous vertebral system draining this latter into the superior caval system. He goes on to say that it seems possible that by means of the connections between the azygos and internal vertebral venous system an explanation may be found for the frequency of the occurrence of metastases from bronchial carcinoma to the adrenal gland. His work has also shown that the filling of the lateral longitudinal sinuses inside the vertebral canal and their tributaries causes an increase in the cerebrospinal fluid pressure; this filling can in its turn be caused by compression of the intrathoracic azygos vein which squeezes blood into the internal vertebral venous plexus and that this appears to be the mechanism of the respiratory variation in cerebrospinal fluid pressure. Franks (1956)<sup>5</sup> on further work states that bone metastases may occur through both vertebral and systemic circulation.

Jeffcoate<sup>8</sup> reporting on a case of intravasation during hysterosalpingography on a patient states that the radiographic appearance would appear to afford conclusive evidence, that even in the reasonably normal woman resting quietly on her back and with no increase in intra-abdominal pressure, some parts of uterus at least can drain into the external and internal vertebral venous channels and that the experience goes to substantiate the probability of this route being sometimes used for the spread of tissue cells, blood clot and organisms from the pelvis to remote parts of the body.

The upper end of the vertebral venous system also plays a part in helping to return venous blood from the cranial cavity in conditions when both the internal jugular veins have to be ligated or partly removed.

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## VERTIGO OF OTITIC ORIGIN

Vertigo is a symptom and not a disease. It is caused by disturbance of those organs of the body that are primarily responsible for body balance, when the posture of the body is erect. The gelatinous substance in the semicircular canals, maculae and saccule begins to flow. This initiates neural impulses that are transmitted to the vestibular nuclei. Impulses from here are transmitted to various parts resulting in the symptom-complex of vertigo :

- (a) Eye muscles leading to nystagmus.
- (b) Cerebellum and skeletal muscles. Righting reflexes.
- (c) Emetic centre—nausea and vomiting.
- (d) Cerebrum. Making one apprise of his position.

The anatomical paths by which these impulses are collected and transmitted by the auditory nerve are well illustrated in Prof. G. Portmann's drawing. Pathologically vertigo has been variously attributed to inflammatory conditions, toxicity, vascular changes, allergy, hydrops, trauma or from disturbances of metabolic or endocrine origin. Nagar<sup>6</sup> opines that the vast majority of cases reveal typical non-inflammatory ectasia of the endolymphatic spaces with varying degrees of neural and sensory atrophy. These pathological changes are associated with the formation or resorption of the endolymph, the aetiology of which despite numerous theories is not yet clearly established. Labyrinthine ectasia was absent in very few isolated cases, which yielded at the same time definite clinical signs of auditory vertigo; these revealed either atrophic degenerative conditions or else no pathological changes whatsoever either of the labyrinth or of the central connections of the eighth cranial nerve; the possibility of various forms of auditory vertigo must therefore be admitted even today, a fact that would greatly affect the chances of successful treatment.

Then there are various other causes disturbing the vestibular apparatus, e.g. deeply sunk wax, tubal obstruction, otitis, acute or chronic labyrinthitis, cerebellopontile angle tumours, arachnoiditis, endocranial manifestations, e.g. abscess, tumour, encephalitis, etc. which require their individual therapy.

With its varied and uncertain aetiology, the treatment has passed through different phases. Babinski<sup>11</sup> advocated lumbar puncture and this was opposed by Quix who advocated decompression of the posterior cranial fossa. Biehl<sup>12</sup> showed that the oval window moves under control of tympanic muscles and the round window under changes of pressure. His operation was to expose the promontory by paracentesis and then opening the window by chisel probe. Late Sir Dundas Grant injected alcohol through the stapes, while Mollison destroyed the labyrinth in non-suppurative aural vertigo by injecting either pure carbolic or pure alcohol. After cleaning the radical mastoid cavity with ether and exposing the bony external semicircular canal, one injects with a blunt lacrimal syringe, one c.cm of absolute alcohol forwards, so that the alcohol may reach the vestibule. The puncture is closed with a temporal muscle graft. Watson Williams<sup>13</sup> does an ossiculectomy; he believed that removal of the incus allowed greater mobility of the stapes which could thus accommodate sudden changes in intralabyrinthine pressure. Out of 17 cases, all got complete relief, while two were untraced.

Modern therapy envisages removal of the causal factor if any with a course of conservative treatment. This comprises correction of all hygienic, dietetic, metabolic, psychotherapeutic, toxic (tobacco) and endocrine factors; a salt-free diet with high protein, low fat and low carbohydrate; fluid restricted to two and a half pints in 24 hours. Histamine phosphate 2.75 mg in 250 c.cm normal saline i.v. given slowly over a period of 1½ hours. If histamine fails, nicotinic acid by mouth or parenterally has been advocated. Cortical steroids have been tried. Vitamin B<sub>6</sub> in dosage of 100 mg parenterally has been recommended by Lewy and Fox. Combination of nicotinic acid in dosage of 25 mg and 25 mg of Thephorin has its advocates. Priscophen—a combination of prisclo and trasentine—is recommended for its action on autonomic nervous system. Portmann advocates cautious use of adrenaline as the best regulator of these autonomic dystonias, given not in fixed doses "but progressively, beginning with 20 drops a day, ten drops at each of two principle meals, to increase by two drops each day, and arrive at a daily dosage of 40 drops, to come back then, diminishing by two drops a day

## Vertigo of Otitic Origin

to the initial dosage of 20 drops per day. Streptomycin therapy is mentioned to be condemned, as vertigo of unilateral origin can obviously not be treated by a drug that will render the patient deaf on both sides. Ultrasonic therapy has been advocated and Portmann claims success in about 60 per cent of his cases.

*Surgical Treatment* : Amesur<sup>1</sup> presented a paper on this subject, before the Indian Medical Association, Karachi, in 1932 and demonstrated some cases. At the Fourth International Congress, Amesur pointed out that the tubal obstruction from whatever cause brings about poor aeration of the middle ear spaces and absorption and thus causes pressure changes, which are communicated to the labyrinth resulting in vertigo. In such cases after removal of the obstruction and dilatation of the tube if the patient does not improve, fibrolysin injections are given, failing which fenestration of the drum in its posterior part is performed under local anaesthesia. If necessary, the tube may be dilated from the middle ear to the nasopharynx. Cawthorn in unilateral cases where the patient is demoralised by frequent attacks and is in danger of losing employment if attacks continued, advocated labyrinthectomy by using his diamond burr, which seems to avoid splinters and the risk of meningitis or of vestibular nerve section. Nylen<sup>14</sup> advocates electrocoagulation application to the posterior aspect of the bony labyrinth at several different points. The intention being to coagulate the vestibular part and to leave the cochlear part intact.

MacNally, Stuart, Mc Kercher and Lockhart<sup>5</sup> reviewed their 200 cases at the London Congress in 1949. Their final impressions regarding surgery were that the surgical elimination of the end-organ should give the most permanent result in unilateral cases. However, the frequent occurrence of cardiovascular and central nervous system diseases in association with dizziness, the frequent failure of surgery to relieve the associated tinnitus and the suggested location of the lesion in vestibular nuclei in streptomycin poisoning—all these suggest that ultimately it may be proved that the lesion is not entirely peripheral. In that case the surgical relief of dizziness except in most selected cases, may be likened to allaying the pain in an acute abdominal emergency, before the correct diagnosis has been made in a patient and the doctor may be lulled into a sense of false security.

Day destroyed the labyrinth by diathermy whereas, experiments of Lindsay and Schlander have shown that intravestibular instrumentation produces extensive fibrosis and degeneration of sensory organs. Ultrasonic methods of treatment advocated by Portmann, Arslan, were by means of an ultrasonic beam to destroy the end organs only, whereas Barbe<sup>12</sup> described a method of ultrasonic therapy without destroying the labyrinth.

The inner ear derives no nerve supply from the tympanic plexus, therefore, operations on this will not benefit. The anatomical basis of Rosen's operation of division of the chorda tympani is not established.

Those who believe that vertigo is a manifestation of endolymphatic hypertension have suggested the opening of the saccus endolymphaticus, which is a prolongation of the membranous labyrinth in the cerebellar dura mater to obtain at this level a filtering scar, permitting the diminution of hypertension. It is the operation of unilateral vertigo in patients with loss of 30 decibels in hearing. Fleet found in 25 per cent of his cases retention of hearing, while in 61 per cent it relieved tinnitus and vertigo and it failed in 14 per cent of his cases. Altman drained the endolymph into perilymphatic space by opening at the vertex of the convexity of the membranous lateral semicircular canal. The labyrinth in a case of hydrops of the endolymph appears to be more easily destroyed than is the healthy labyrinth in otosclerosis or in cases of vertigo following mastoidectomy.

The role of the autonomic nervous system in the efficient working of the labyrinth has been well recognised; section of cervical sympathetic, extirpation of the cervical sympathetic ganglions and pericarotid sympathectomy have been practised by Portmann<sup>8</sup> with some but not lasting results.

The late Garnett Passe<sup>7</sup> and Seymour suggested that vasoconstriction of the labyrinthine blood vessels caused vertigo. They cured 12 cases with cervical sympathectomy. Further improvements were published on behalf of the late Garnett Passe in 1951 and again in 1953 in which was stressed the importance as well as, the difficulty of establishing a correct diagnosis. M.R.D. did pre- and post-operative observations in five cases operated by late Garnett Passe, by upper dorsal sympathectomy. His conclusions were that the operation had a beneficial

effect on vertigo and to a lesser extent on tinnitus, but is variable in its effect on deafness. It may well be that the primary disturbance of endolymph circulation though not caused by vasospasm is nevertheless corrected by vasodilatation in a manner not at present understood.

Lewis<sup>1</sup> mentions that in some cases there is a return of sympathetic activity which is probably due to re-routing of impulses through accessory sympathetic paths in the minute Skoog ganglion. Cawthorne<sup>3</sup> who has done this over a fair length of period says that Mènière's vertigo may be the Achilles' heel of the endolymphatic system about which we have still a great deal to learn.

Lastly section of the auditory nerve at the level of its penetration into the endocranium was advocated by the late Marriage and Cuthbert Wallace which was again revived later by Dandy and others. The operation has obvious drawbacks as one is not always sure of preserving the facial nerve and much less sure that the section would be limited to the vestibular fibres to the exclusion of the fibres of the cochlear. Nothing would justify such an operation except as a last resort in case of failures of all other methods.

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#### VITAL STATISTICS

A. K. Niyog†

*Bombay State* : The Annual Public Health Report<sup>1</sup> of the Bombay State for 1955 showed that the crude birth rate during the year rose to 37.2 from 26.5 for the previous year. The crude death rate was 15.2, which is lower than the average of the previous five years' figure of 16.5. However a look at the number of births and deaths among 2.4 million population in the whole state, shows that in that sample crude birth rate was 43.2 and crude death rate was 19.4. It brought the important point that 17 per cent of births and 10 per cent of deaths in that sample were not registered—a fact which has to be considered for any year-to-year evaluation of the condition of the health in the state.

The report showed that the infant mortality rate had declined to 100 from 109 in 1954 and the rates for urban and rural areas were 98 and 100 respectively. The maternal mortality rate was 4.8 as against 4.3 in 1954.

Among the cause of death, fevers and malaria showed further decline to 5.4 per 1000 population which is nearly half the figure for 1921. The spectacular effect of D. D. T. spraying on the incidence of malaria is continuing in North Kanara district, now in Mysore State, and showed a spleen rate of 0.0 per cent in 1954 and 1955. In other districts also the spleen rate in 1955 was a very small fraction of the pre-D.D.T. years. The number of deaths due to respiratory diseases remained steady since 1951 at 2.5 per 1000 estimated population, after a decline from 5.7 in 1941-51, a fact which appears to be more the result of the use of antibiotics. Cholera caused 289 deaths during 1955, in which year, it is lying at the bottom of the intercrestal trough. Small-pox killed 2419 people. Seventy-two per cent of these deaths were among the children of age group 0-10 years, and 30 per cent among 0-1 year. High pressure vaccination programme was carried out and since 1954 and upto 1955, one-fourth the total population of the state was vaccinated. If the coverage of infants and children can be given and the intensive programme continued the disease is likely to be eliminated within few years. Omitting the absentees, out of 4.8 million people tested with tuberculin, 1.5 million were found negative of

## Vital Statistics

whom 85 per cent were vaccinated with B. C. G. These are remarkable results considering the individual type of service required to be given and the widely spread out villages where it was offered.

A schistosomiasis survey was made in the village Gimvi in Ratnagiri district; out of 528 individuals examined, 38 were found infected. In other villages around Gimvi, no infected persons could be detected. Majority of the individuals examined were children. 78 primary health centres were opened in villages during the year and each was staffed by a medical officer, a health visitor or a nurse cum midwife and a midwife, the latter two with public health training. Maternity homes were provided in some of them. Opening of primary health centres is an outstanding event in the development of health services in any country because it marks the beginning of a rational and positive approach towards health. The effects of these centres on the health of the population will be a matter of much interest to all.

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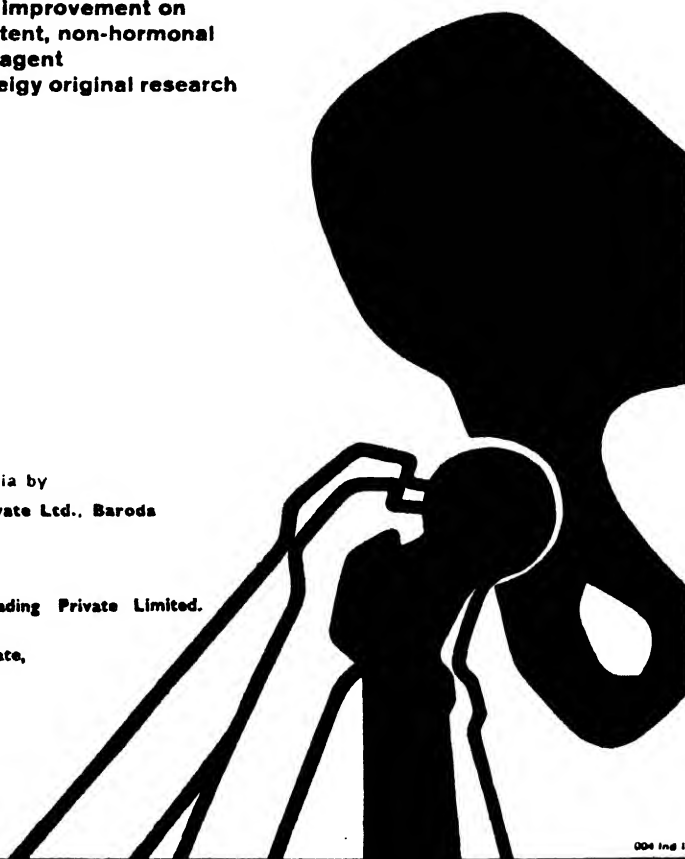
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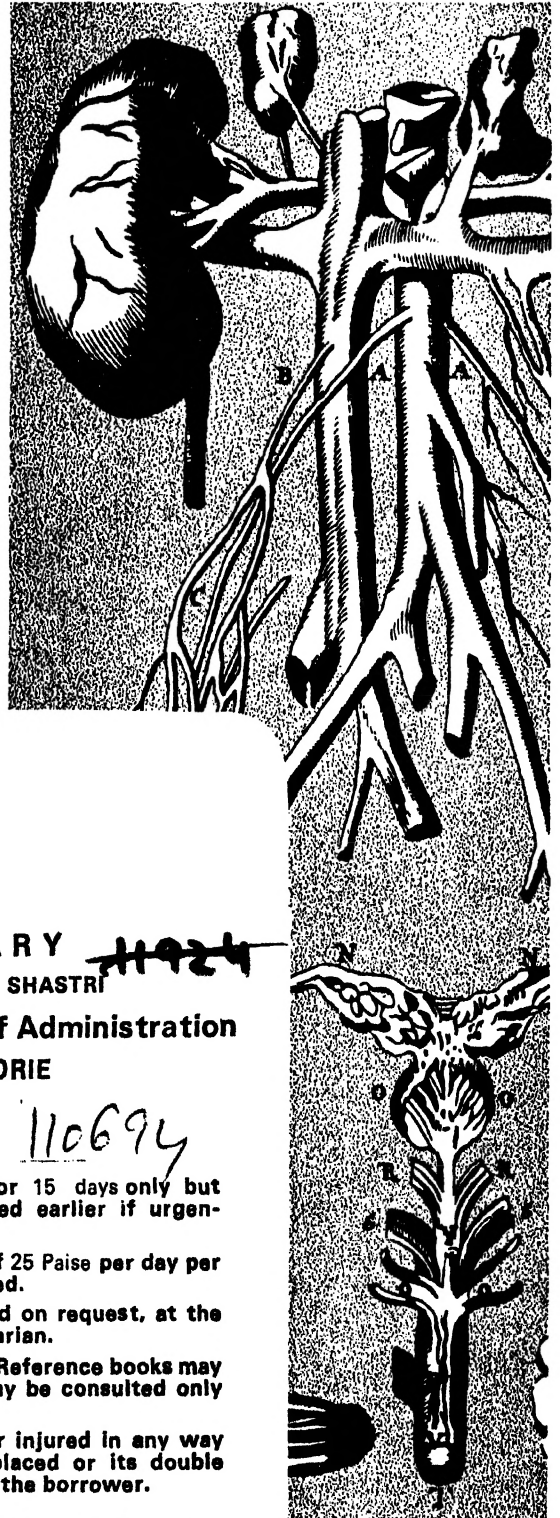
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